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CANCER OF THE CHEEK (BUCCAL MUCOSA)

STUDY OF NINETY-NINE CASES WITH RESULTS OF TREATMENT AT THE END OF FIVE YEARS

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During the five year period from 1925 to 1929, ninety-nine cases of carcinoma of the cheek the records of which are sufficiently complete to form a basis for this clinical study were observed in the clinic at Memorial Hospital. This series includes all of the cases of cancer of the cheek, in both the early and the hopelessly advanced stage, in which we had histologic proof of the presence of cancer, and in which there was subsequent observation for at least one month or until death. We excluded those cases in which the disease was not proved histologically, for instance, those in which, although the condition clinically appeared to be cancer, papilloma only was revealed on histologic examination. We also excluded the cases of those patients ("clinic shoppers") who made but one or two visits to the clinic and were then lost track of within one month, without receiving the proffered treatment. The reported end-results are based on the histories of patients observed for five years or longer. Since we have included the cases of hopelessly advanced disease (thirty-two, or 32 per cent) in which palliative treatment only was given, we offer this report as an index of the disease as it is seen at the time when the patients first apply for treatment. Twenty-four patients (24 per cent) had received unsuccessful treatment by surgical excision, cautery or irradiation previous to their application at the clinic. In the case of nine of these, local surgical excision of the primary lesion had been made.

ETIOLOGY

Carcinoma of the cheek (buccal mucosa) comprises 9.5 per cent of all of the intra-oral tumors (Pack and Le Fevre [1]). In this group of

Read at a meeting of the American Radium Society, Cleveland, June 1934.

1. Pack, G. T., and Le Fevre, R. G.: The Age and Sex Distribution and Incidence of Neoplastic Diseases at the Memorial Hospital, New York City, J. Cancer Research **14**:167, 1930.

neoplasms, it ranks third in frequency, cancer of the tongue (20.6 per cent) and cancer of the lip (15.4 per cent) being the most common forms. It is chiefly a disease of old age and is seen less often in young people than is any other form of intra-oral cancer. The average age of the patients in our series was 59. The oldest patient was 97 and the youngest 33. About 50 per cent of the cases occurred in the fifth and sixth decades of life. The disease is over nine times as frequent among men as among women. Nine cases only, or 10 per cent, in our series occurred in women.

The right and the left cheek were involved in almost the same number of instances; it seems that findings such as those of Steiner,[2] who reported that in 70 per cent of thirty-three cases the disease was noted on the left side, are purely accidental. The midportion of the cheek, opposite the occlusal level of the teeth, is the site most often involved (40 per cent), although the disease may appear at any point on the buccal mucosa or in either of the buccogingival grooves. A considerable number of carcinomas arise just posterior to the labial commissure. Direct local extension of the primary growth into the adjacent soft parts may take place early in the course of the disease. Local extension of this kind was found at the time of admission to the clinic, in over 60 per cent of our cases.

Chronic irritation is a more obvious etiologic factor in carcinoma of the cheek than in any other type of intra-oral cancer. The most common chronic irritants to the buccal mucosa are sharp or broken teeth, ill-fitting dental appliances, syphilis and tobacco. The last agent acts both by the production of local heat and by chemical irritation. Davis [3] attributed the prevalence of carcinoma of the cheek in the Philippine Islands to the chewing of buyo, which is a combination of buyo leaf, betel nut, slaked lime and tobacco—a habit most common among the Philippine women. It is interesting to note that Davis reported the incidence of cancer of the cheek as greater among women than among men. We found definite evidence of dental irritation in twenty-three cases (23 per cent), either from sharp teeth or from ill-fitting dentures.

Leukoplakia is a common precancerous response of the mucous membranes composed of flat pavement epithelium to chronic irritations. Intra-oral leukoplakia occurs most often in the mucosa of the cheek; it was specifically noted in 22 per cent of the accompanying cases. In a special investigation of the incidence of leukoplakia among the cases of intra-oral cancer in our clinic, the condition was found in about 70 per cent of the cancers of the cheek. Carcinoma may arise in a patch of

2. Steiner, P.: Beiträge zur Krebsstatistik, Deutsche Ztschr. f. Chir. **24**: 363, 1906.

3. Davis, G. G.: Buyo Cheek Cancer, J. A. M. A. **64**:711 (Feb. 27) 1915.

leukoplakia or in apparently normal mucous membrane adjacent to a patch of leukoplakia. In susceptible persons chronic irritation may produce either cancer or leukoplakia or both, and in certain instances the leukoplakia may undergo malignant change. We have observed cases of generalized intra-oral leukoplakia for from ten to twelve years without noting a malignant change.

As a chronic irritant, syphilis, in the form of syphilitic glossitis, is a predisposing factor in all of the anatomic varieties of cancer of the oral cavity proper. Wassermann tests, made in thirty-eight of our cases, gave positive results in six, or 15 per cent.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is not ordinarily difficult. In all of the cases in which cancer of the oral cavity is suspected, a biopsy should be made at the time of the first examination in order to verify the clinical diagnosis.

The diseases other than cancer which most commonly present ulcerated lesions of the buccal mucosa are syphilis, tuberculosis, superficially ulcerated or fissured leukoplakia, herpes and simple granulomas (trauma, Vincent's angina and so on).

Syphilitic lesions may exactly simulate cancer in their clinical appearance. A correct diagnosis is obtained only if repeated biopsies fail to reveal the presence of cancer, if the Wassermann reaction is positive and if the lesion disappears after two or three weeks of intensive antisyphilitic treatment. A positive Wassermann reaction alone does not disprove the presence of cancer. The two diseases coexist in a large percentage of cases.

Tuberculous ulcers may occur on the buccal mucosa, but they are more common on the tongue. Such ulcers usually present a yellowish, unhealthy base, as compared to the coarse, granular appearance of cancerous lesions; they are more likely to be tender and painful. The diagnosis is made by the aid of biopsy (preferably repeated) which fails to show the presence of cancer, roentgen examination of the chest and examination of the sputum. Tuberculous ulcers of the oral mucous membranes are almost invariably secondary to demonstrable pulmonary tuberculosis.

Long-standing leukoplakia of the cheek may present superficially ulcerated or fissured areas which are prone to undergo malignant change. Tissues for biopsy should always be taken from such suspected areas. Local treatment by irradiation or by cautery should be given in all of these cases, despite failure of biopsy to reveal cancerous tissue.

A definite diagnosis of simple granuloma should never be made without repeatedly negative results of biopsy. The biopsy may be withheld temporarily if there is a history of recent adequate trauma, such

as the biting of the cheek, or if a painful, tender ulcer, such as those present in herpes or in Vincent's disease, suddenly appears. If such an ulcer persists longer than two weeks, a biopsy is definitely indicated.

PATHOLOGIC LESIONS

By histologic examination, cancer of the cheek is found to be epidermoid carcinoma in 95 per cent of the cases. Adenoid tumors may arise from minor salivary glands of the buccal mucosa. One case of myxosarcoma occurred in the present series. In table 1 the distribution of the histologic types of carcinoma of the cheek among the successfully

TABLE 1.—*Distribution of Ninety-Nine Cases of Cancer of the Cheek on the Basis of the Histopathologic Type and Malignancy of the Neoplasm and the Number and Percentage of Cures*

Type of Cancer	Number of Cases	Cures at End of Five Years
Epidermoid carcinoma, grade I	38	15 (39%)
Epidermoid carcinoma, grade II	53	11 (20%)
Epidermoid carcinoma, grade III	3	0
Adenocarcinoma	4	2
Myxosarcoma	1	0
Total number of cases of all types	99	28

and the unsuccessfully treated groups is recorded, and the prognostic significance of tumor grading is indicated. It is to be noted that 39 per cent of grade I tumors were controlled for five years or longer, but that only 20 per cent of grade II tumors so responded.

SYMPTOMS

In common with all types of cancer, carcinoma of the cheek is essentially symptomless in its early stages. It first appears as a small, ulcerated, indurated mass, which may or may not protrude above the surface of the mucosa. Unless the lesion begins in the center of the cheek, the tendency is toward an early invasion of the upper or the lower jaw, the lateral pharyngeal wall or the palate. It seems that, with the assistance of the acute tactile sense of the tongue, the presence of a roughened area or ulcer on the sensitive mucosa of the cheek should be easily noted, but such signs are at first almost always disregarded, and the patient thinks that he has unconsciously bitten his cheek or that he has a "canker sore." By one who is careless of oral hygienic care, the irritation of a sharp tooth is as complacently disregarded and neglected as are the decay and loss of the teeth themselves. In only about 8 per cent of the cases in our series was the primary lesion, at the time of admission, less than 2 cm. in diameter, and in about 30 per cent it was between 3 and 4 cm. About one third of the patients reported "sore-

ness" as the first symptom, which indicates that no particular attention was paid to the presence of the lesion until it was far advanced and deep fissuring infection or even sloughing had occurred. The other two thirds of the patients complained of no symptom but the presence of the lesion.

The average duration of the symptoms, according to the statements of the patients, was nine months, and in only eighteen cases (18 per cent) did the history of symptoms cover less than two months. In two cases, the patient had sought medical advice because of enlarged cervical nodes. In one of these cases a biopsy had been made on material from a cervical node, after which the patient was referred to the Memorial Hospital with the diagnosis of "squamous carcinoma of the neck." The mouth was in a fetid condition, owing to a massive, fungating, necrotic tumor of the cheek, which the patient had apparently not considered worthy of mention.

TABLE 2.—*Local Extension of Carcinoma of the Cheek at the Time of Admission in a Series of Ninety-Nine Cases*

Location of Extension	Number of Cases
Upper jaw alone	7
Lower jaw alone	18
Both upper and lower jaws	8
Mucosa over ascending ramus of mandible	11
Upper jaw and mucosa over ascending ramus of mandible	4
Lips	13
Total number of extensions	61

Direct extension of the primary lesion into the adjacent soft parts is common and may occur early in the course of the disease. In sixty-one (61 per cent) of the cases at the time of admission extension had taken place beyond the mucosa of the cheek, as indicated in table 2.

This early tendency toward the invasion of the neighboring structures suggests at once the unsuitability of the disease to surgical measures for the control of the primary lesion and it explains the indifferent surgical results reported in the literature. Extension to the lower jaw alone or to the lips might be dealt with by extensive surgical procedures, but the involvement of the lateral pharyngeal wall or of the palate offers little chance of control, even by the most extensive surgical intervention.

As the tumor enlarges, it becomes fissured and necrotic from the trauma involved in stretching the cheek and in biting during mastication. Infection takes place, followed by swelling of the cheek and tenderness or pain. As the cheek becomes infiltrated by the growth and as infection develops, its elasticity is lost, and mastication and the opening of the mouth are interfered with. If the growth is located posteriorly, so that

the infiltration and the infection occur in the neighborhood of the pterygoid and temporal muscle and their tendons, trismus ensues. The tumor may fungate into the mouth and form an oozing, sloughing, fetid mass, or it may perforate the cheek and appear externally on the surface of the skin. Extension may occur, either early or late, to the upper or the lower jaw, backward into the pharynx or anteriorly into the angle of the mouth or into the upper or the lower lip. Unless the disease invades the upper or the lower jaw, through sockets of teeth, invasion of the bone is apt to be a late manifestation, for the normal periosteum is resistant to the local extension of a carcinoma. In the untreated patient, the tumor usually tends to perforate the skin of the cheek and extend directly to the upper and the lower jaw.

Eventually, local infection, pain and trismus appear. Metastasis to the submaxillary lymph nodes with mixed infection complicates the clinical course. Hemorrhage from erosion of the internal maxillary or facial artery may take place. Death ensues from a combination of causes: infection, pain, malnutrition and hemorrhage. As is the case in most forms of intra-oral cancer, the disease usually causes death without progressing below the clavicle.

METASTASES

Metastases tend to occur comparatively late in the course of the disease. In this series, despite the fact that the average duration of symptoms prior to admission was nine months, fifty-six patients (56 per cent) had no palpable nodes at the time of admission. In at least fifty-one (51 per cent) but in not more than fifty-six, metastases developed at some time during the course of the disease, and in all but eleven of these the submaxillary lymph nodes only were involved. In all but one of the patients with metastases occurring beyond the submaxillary triangle, the primary lesion was posteriorly located and had extended backward into the tonsillar region, and the metastases had occurred to the upper deep cervical nodes.

With the exception of the eleven cases just mentioned and of one to be noted later, the disease did not extend beyond the submaxillary triangle, and it was controlled or the growth was limited to the cheek, the contiguous structures and the submaxillary triangle at the time of death. In two cases, there was metastasis bilaterally to the submaxillary triangle; in each of these instances extension, anteriorly, had taken place across the midline into the upper lip. In one case of bilateral metastasis, death was due to metastasis to the liver (observed at autopsy); in another, in which the primary lesion was situated posteriorly, widespread metastases occurred to the skin of the thoracic wall, following a radical dissection for the involvement of the submaxillary and the upper deep

cervical lymph nodes. In these two cases appeared the only extensions below the clavicle. As a general rule, the disease does not extend beyond the submaxillary triangle, an observation of great importance in dealing with metastases to the nodes of the neck. Its significance is further discussed in connection with the treatment.

TREATMENT

We are of the opinion that the most successful treatment of carcinoma of the cheek is by a combination of irradiation and surgical intervention. From the published results, it appears that surgical treatment alone is far less successful in this disease than in cancer of the lip and of the tongue. We shall subsequently discuss the surgical aspects at greater length.

TABLE 3.—*Occurrence and Treatment of Metastases in Ninety-Nine Cases of Cancer of the Cheek*

Patients with metastases:	Number
Present at time of admission	43
Appearing after time of admission	8
Total	51 (51%)
Of possible later occurrence in patients who died of the disease but were not continuously observed	5
To submaxillary triangle only	40
To submaxillary triangle, upper deep cervical nodes or beyond	11
Bilaterally to submaxillary triangle	2
Below clavicle	2
Metastases present at some time during course of disease in twenty-eight successfully treated patients	9 (33%)
Treated by irradiation and neck dissection	6
Treated by irradiation alone (external irradiation and by implants of radon)	3

At the outset, one should decide whether the treatment is to be an attempt at cure or to be merely palliative. In the case of far advanced disease, any attempt at cure usually increases the suffering and shortens life. If treatment by irradiation is instituted, the quantity of radon in the implants necessary to produce complete regression is practically in direct proportion to the volume of the neoplastic mass, and the surgeon must first decide whether a curative dose of this size will be reasonably well tolerated by the patient.

In the treatment of cancer of the cheek, three distinct problems must be considered: the hygienic care of the oral cavity before and during the treatment, the treatment of the primary lesion and the management of the cervical metastases.

General Hygienic Measures.—In most instances, the hygienic condition of the oral cavity is poor, and this complication is always increased temporarily during the treatment by irradiation. Decayed or sharp teeth, coated with epithelial débris, are almost always present.

Before instituting treatment, prompt measures must be taken to improve the oral hygiene. A sharp tooth, especially if in contact with the lesion, should be filed smooth or possibly extracted, but the wholesale extraction of teeth should be avoided, as the attendant laceration of the gums temporarily increases oral sepsis and delays treatment. The extraction of teeth following heavy irradiation is so commonly followed by osteomyelitis that in spite of the chances of the local spread of the disease we often advise the extraction of a limited number of condemned teeth.

In all of the cases, the surfaces of the teeth should be thoroughly cleaned by a dentist, and the patient instructed in the use of a toothbrush, with which he is apt to be unfamiliar. As a mouth wash, compound solution of sodium perborate, should be used, and copious irrigations with saline solution are of great value until the reaction from irradiation has subsided. We usually insist on daily visits to the clinic during the first few weeks of treatment, at which times the oral cavity and the interstices between the teeth are cleansed with a power spray of surgical solution of chlorinated soda, U. S. P. A vigorous combating of the oral sepsis is of great value in conserving the general strength and the nutrition during what may be a trying period.

Treatment of the Primary Lesion.—The primary lesion should be treated almost entirely by irradiation. In the series here reported on, the plan was first to give one application of external irradiation. In most cases, roentgen radiation (200 kilovolts and a filter of 0.5 mm. of copper and 1 mm. of aluminum) was given to the affected side in a dosage of from 600 to 700 r units (roentgens) at a distance of 50 cm. The skin portal included the primary lesion and the submaxillary triangle. In a few cases, the radium element pack was used to deliver about the same skin dose at a distance of 6 cm. This dosage was ordinarily a little more than 1 skin erythema dose; by this means, a diffuse depth dose was delivered both to the primary lesion and to any possible metastasis. Following this, a tray with an area of 20 sq. cm., and a filter of 2 mm. of brass, at a distance of 3 cm., was applied externally to the cheek opposite the primary lesion, and a dose of from about 2,500 to 3,000 millicurie hours given. This application was directed chiefly locally to the base of the primary lesion, as it were, attacking it from beneath. These two procedures by the use of external irradiation are almost always applicable, and were employed more or less as a routine in our technic. At the present time, we give the external radiation through the cheek to the primary lesion in multiple divided doses, but since this technic was not used in the series reported here, it is not described in detail at this point.

Following external irradiation, interstitial irradiation was employed in the form of gold implants (with a filter of 0.3 mm. of gold), which

were inserted into the primary lesion. With this method we prefer implants, rather than needles, owing to the difficulty, or often the impossibility, of maintaining the latter in position in a thin or a fragile mass. After a careful measurement of the primary lesion with calipers, an applicator dose of gold seeds is prescribed, which delivers from 7 to 10 skin erythema doses to the neoplastic mass (table 4). In this measurement, the mass is considered as a sphere the diameter of which is equal to the longest diameter of the primary lesion. In growths of very irregular shape, two or more adjacent or overlapping spheres may be considered, and the dose for each calculated separately. A more detailed discussion of this method for the calculation of the dosage has been published by one of us (Dr. Martin [4]). The number of millicuries of radon in the gold implants necessary to produce the specific

TABLE 4.—*Millicuries of Radon in Gold Seeds Required to Deliver Specified Skin Erythema Doses to Tumors of Various Diameters*

	Diameter of Mass, Cm.											
	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
Skin Erythema Doses	Millicuries of Radon											
1	0.2	0.5	0.8	1.5	2.0	2.4	2.9	3.4	4.0	5.4	7	9
2	0.4	1.0	1.6	3.0	4.0	4.8	5.8	6.9	8.0	11	14	18
3	0.6	1.5	2.4	4.5	6.0	7.2	8.7	10	12	16	21	27
4	0.8	2.0	3.2	6.0	8.0	9.6	12	14	16	22	28	36
5	1.0	2.5	4.0	7.5	10	12	14	17	20	27	35	45
6	1.2	3.0	4.8	9.0	12	14	17	20	24	32	42	54
7	1.4	3.5	5.6	10	14	17	20	24	28	38	49	63
8	1.6	4.0	6.4	12	16	19	23	27	32	43	56	72
9	1.8	4.5	7.2	14	18	22	26	31	36	49	63	81
10	2.0	5.0	8.0	15	20	24	29	34	40	54	70	90
11	2.2	5.5	8.8	17	22	26	32	37	44	59	77	99
12	2.4	6.0	9.6	18	24	29	35	41	48	65	84	108
13	2.6	6.5	10	20	26	31	38	44	52	70	91	117
14	2.8	7.0	12	21	28	34	41	48	56	76	98	126
15	3.0	7.5	13	23	30	36	44	51	60	81	105	135

tissue doses in masses of various diameters are given in table 4. All of the irradiation should be completed in from seven to fourteen days.

The technic just described is designed for the primary lesion as usually seen, and in these cases, except for the hygienic care already mentioned, no further therapeutic measures are taken.

In this series, the largest dose of radon gold seeds given to a sucessfully treated patient was 20 millicuries. The doses most frequently used with success ranged between 8 and 16 millicuries (figs. 1 and 2).

In certain instances, often not in the most malignant cases, the growth tends to fungate into the mouth rather than to infiltrate the cheek deeply. In such cases, the period of convalescence is shortened by removing the tumor mass to the level of the mucosa by actual cautery

4. Martin, H. E., and Quimby, E. H.: Calculations of Tissue Dosage in Radiation Therapy, Am. J. Roentgenol. **23**:173, 1930.

about a week or ten days following the interstitial irradiation. By this procedure, the implants are removed before they have delivered their total energy; their initial quantity, therefore, should be correspondingly greater.

As already mentioned, at the present time we are giving the external irradiation through the cheek to the primary lesion in multiple divided doses of roentgen radiation, rather than by the use of the single dose of roentgen rays and the radon tray. About 2,500 to 3,500 r units are given in from ten to fifteen divided doses over a period of from two to three weeks, with a circular skin portal 7 or 8 cm. in diameter. We are of the opinion that this technic is of great value, since the primary

Fig. 1.—*A*, squamous carcinoma of the cheek, grade I, diagnosed at biopsy. Treatment was administered by a radon tray, with an exposure of 3,000 millicurie hours at a distance of 3 cm., and by the implantation of 15 radon gold seeds of 20 millicuries in the primary lesion; *B*, complete healing of the lesion with no recurrence of the disease after five years.

lesion often diminishes markedly in size and requires a lesser dose of radon seeds than would otherwise be required. The decision as to when the external irradiation should be discontinued and the seeds implanted must be guided by clinical experience, but the implantation should follow almost immediately the external irradiation. We have in a few instances obtained complete regression of the primary lesion in the cheek by divided doses of roentgen radiation alone; usually, however, the growth is too resistant to the roentgen rays for successful control by that method alone, and in most cases we advise against the attempt.

Treatment of Metastases.—This problem should be considered separately. If no nodes are palpable at the time of admission, we usually give one treatment by external irradiation to the cervical region, following which no further treatment is given to the neck until definite palpable evidence of the presence of metastases appears.

We are opposed to prophylactic neck dissection.[4a] The validity of this view is evident from the statistical data obtained in this study. In at least 44 per cent of the cases metastases developed at no time during the course of the disease, and in fifteen

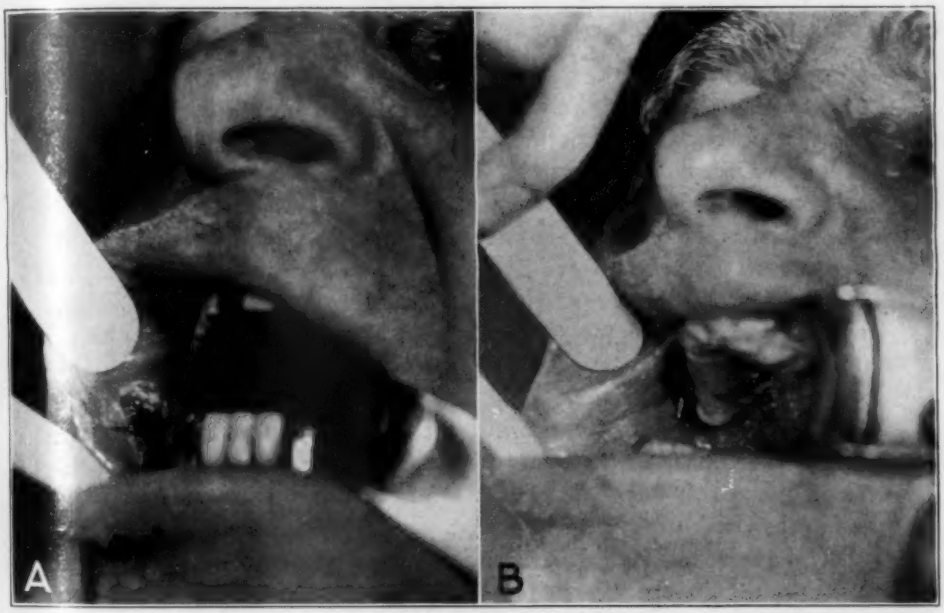

Fig. 2.—*A*, squamous carcinoma of the cheek, grade II, diagnosed at biopsy. Treatment was administered by a radon tray, with an exposure of 3,000 millicurie hours at a distance of 3 cm., and by the implantation of radon gold seeds of 5 millicuries into the primary lesion; *B*, complete healing of the lesion with no recurrence after five years.

cases death is known to have occurred from local extension of the disease, but without metastases. Of the twenty-eight successfully

4a. By neck dissection we mean the removal of all lymph node-bearing tissue between the skin and the deep muscle fascia of the neck from the lower edge of the mandible to the clavicle and from the anterior border of the trapezius to the midline of the neck, including the submaxillary salivary gland, the sternocleidomastoid muscle, the superficial veins and the jugular vein. By submaxillary dissection we mean the removal of all lymph node-bearing tissue between the skin and the deep muscle planes of the submaxillary triangle, including the submaxillary salivary gland.

treated patients, twenty-four (85 per cent) were without palpable nodes at the time of admission. Of the twenty-four, five (20 per cent) presented metastases within from three months to one year. In no case did metastases develop later than one year following the control of the primary lesion. Of the fifty-six patients presenting no metastases at the time of admission, among whom are included both those successfully and those unsuccessfully treated, in only eight, or 14 per cent, did metastatic nodes of the neck appear later. Routine prophylactic neck dissection would therefore have necessitated fifty-six operations in order that possible benefit might result in eight cases. It appears that no further proof is required to demonstrate the lack of justification for the employment of prophylactic neck dissection in cases of cancer of the cheek.

If metastases are present at the time of admission, our usual procedure is either to perform a neck dissection after the control of the primary lesion or to insert gold seeds after the surgical exposure of the nodes by a short incision through the skin and superficial tissues only. This exposure permits a more accurate measurement of the node, which is essential in the determination of the dosage and, furthermore, permits an accurate placement of the implants. Quick [5] has published the technic which we employ in the combined surgical and radiologic method of treatment of metastatic nodes of the neck. Neck dissection or any extensive surgical procedure is to be avoided, if possible, during the aggressive irradiation of the primary lesion. If metastases appear for the first time, or additional nodes become palpable after the subsidence of the reaction from radiation in the cheek, we have, in the past, performed a submaxillary dissection on the affected side. In this series, we performed dissections of the cervical nodes in twenty-three cases. In six of these, there was no recurrence, either in the cheek or in the neck. In twenty-eight cases the metastases were treated by irradiation alone in the form of external irradiation and radon seeds inserted either through the skin or after limited surgical exposure. In seven of these complete regression without recurrence took place, although four patients died of local extension of the primary lesion. Since the specific form of therapy for the surgically treated and irradiated groups of metastases was chosen to suit the particular case, we do not think that the statistics just cited necessarily present a fair picture of the relative merits of surgical treatment and irradiation. The cases chosen for neck dissection were those in which the primary lesion was under control and in which cervical nodes were freely movable and oper-

5. Quick, D.: Interstitial Radiation in Metastatic Cervical Nodes of Epidermoid Carcinoma, Ann. Surg. **93**:380, 1931.

able. The metastases which were treated by irradiation only in most cases were fixed and inoperable or occurred in those patients in whom the primary lesion was extensive. In the patients treated palliatively, all of the metastases were given irradiation only. Of late, we have tended to depend more on the use of interstitial implants in the treatment of enlarged nodes of the neck.

It should be realized that in many of the moderately advanced cases, in which the average age is about 60, the general condition of the patient may necessitate wide variations in management. Invasion of the mandible by the primary lesion or the attachment of metastases to the bone may require resection of a portion of the mandible. This was done in two of the cases. If a submaxillary node has not perforated its capsule but has become definitely attached to the mandible, it may often be removed with the attached bone by the excision of the crescent-shaped portion of the mandible only. Severing of the continuity of the mandibular arch is thereby avoided.

COMPLICATIONS

In case of hemorrhage from erosion of the facial artery by an extensive uncontrolled primary lesion, ligation of the external carotid artery may be necessary.

Local necrosis of the soft tissues of the cheek sometimes follows heavy irradiation. It seldom extends through the entire thickness of the cheek, and if the growth has been controlled it does not seriously alter the end-result, although it may delay healing. Local necrosis in this series was not definitely associated with the use of large doses of radon implants, and we are of the opinion that the most common causes of local breaking down of the tissues are the poor distribution of the implants and the unnecessary introduction of infection during the procedure of implantation. In certain cases, local necrosis of the cheek followed the neck dissection, during which the facial artery is always severed.

Osteomyelitis of the mandible may follow the heavy irradiation of extensive disease in the lower gingivobuccal gutter or its extension to the lower jaw. If osteomyelitis does not involve the entire cross-section of the mandible, conservative treatment is indicated, awaiting the separation of the sequestrum. If osteomyelitis has involved the entire cross-section of the lower jaw, resection of a portion of the mandible may be indicated. The operation is performed through the mouth without skin incisions; external scarring and injury to the facial nerve are thereby avoided. The procedure is followed by less deformity than might be expected if the anterior portion of the mandibular arch and the anterior attachments of the two digastric muscles can be spared.

In resecting a portion of the horizontal ramus, we remove as well the ascending ramus, which, if left by itself, is a mechanical nuisance and delays healing. We have considered that operations of bone grafting were seldom applicable within the five year period following the treatment of such a lethal disease as cancer of the cheek.

PROGNOSIS AND RESULTS OF TREATMENT

Morestin [6] stated that carcinoma of the cheek has the worst prognosis of any of the intra-oral cancers, whereas New [7] and Brewer [8] have even declared that its malignancy is exceeded only by that of melanoma. With these opinions we cannot agree. Polya [9] expressed the opinion that cancer of the cheek is more malignant than that of the lip but less malignant than that of the tongue. Under proper treatment, the prognosis of carcinoma of the cheek should be about the same as that of cancer of the lip, were it not for the fact that cancer of the lip is usually discovered earlier in the course of the disease, with a consequent lessened chance of metastases and with the primary lesion more amenable either to irradiation or to surgical treatment. This advantage is somewhat counterbalanced by the tendency of metastases from cancer of the lip to advance bilaterally or beyond the submaxillary triangle. Carcinoma of the cheek metastasized beyond the submaxillary triangle in only about 10 per cent of our cases, but the primary lesion is usually more advanced and is not so accessible either to surgical measures or to irradiation. Histologically, cancer of the cheek and that of the lip are similar.

As compared to cancer of the lip and of the tongue, there are relatively few strictly surgical observations and statistics on cancer of the cheek in the literature. The few surgical statistics which have been published are incomplete and unsatisfactory as to the period of observation and the method of the selection of cases. From surgical treatment alone the only results at the end of five years which we have been able to find reported are those of Simmons,[10] who, from a selected group of thirteen patients in all of whom there were no metastases at the time of admission, reported six patients (48 per cent)

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6. Morestin, H.: Cancer de la joue, Rev. gén. de clin. et de thérap. **14:** 516, 1900.

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as living and free from disease after five years. Simmons' report would have been of real value had he included the results in the patients with metastases at the time of admission as well as those in the patients with cancer in hopelessly advanced stages.

Steiner's [2] report, published almost twenty years ago, included a series of thirty-three consecutive unselected cases. Seventeen of the patients were operated on, and three (9 per cent) remained free from disease for three years. At various times, Morestin [11] reported twenty-six cases with operation, with three (11 per cent) of the patients free from disease for three years. Boyd and Unwin [12] reported that four of ten patients were apparently cured three years after operation. The following authors reported a total of seventy-nine cases with no cures: Warren,[13] eight; Brewer,[8] eleven; Bradfield,[14] seven, and Davis,[3] fifty-three. All the aforementioned reports, except Steiner's, were based on groups of cases selected because of operability, and are therefore of no value from the comparative standpoint.

The published results obtained from irradiation, or from a combination of irradiation and surgical intervention, are much more encouraging. Schreiner and Simpson,[15] using irradiation only, reported thirty cases, among which were six cures (20 per cent) at the end of five years. Regaud [16] reported 19 per cent of cures at the end of five years among forty-seven patients treated by irradiation, and Berven,[17] twenty-one among eighty-one patients (26 per cent) who were free from disease for five years or longer.

The results obtained in the ninety-nine cases of this study are tabulated in table 5. Of the entire group, twenty-eight patients have now been free from disease for from five to eight years.

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These figures were based on a representative group of patients with carcinoma of the cheek admitted to the Memorial Hospital. In this group are included the patients with advanced disease who were admitted for palliative treatment and for observation. In about 70 per cent of the cases with fatal outcome, the patient died within one year after the first symptom, death in one instance occurring within four months. The case of longest duration among these patients was one of two and one-half years.

The primary lesion was controlled in forty-six cases, or in almost one half of the total number, so that the patients either remained free from disease or died of metastases without the local recurrence of the primary lesion. With the exclusion of the cases of advanced disease in which palliative treatment only was given, we succeeded in controlling the

TABLE 5.—*Results at the End of Five Years in the Ninety-Nine Cases of Cancer of the Cheek*

Status of Patient	Number
Dead as result of cancer of cheek	57
Lost track of with disease (probably dead)	3
Living with recurrence of primary lesion	1
Total number of failures in treatment	61
Indeterminate group	
Dead as result of other causes and without recurrence (two after one year; two after two years and one after four years)	5
Lost track of, without recurrence (one after one year; one after two years, and one after four years)	3
Total number of indeterminate results	8
Total number (99) minus those of indeterminate group	91
Free from disease after from five to eight years	28
Cures after five years	30 per cent.

primary lesion in forty-nine of sixty-seven (73 per cent) attempts at cure. It is therefore evident that once the disease has metastasized to the neck, its control becomes far more difficult.

Although the 30 per cent of cures at the end of five years is not satisfactory, it is a marked improvement over the results noted in most surgical statistics. Surgical intervention in carcinoma of the cheek is distinctly a major procedure. The operative mortality is high (Steiner, 11 per cent; Warren, 25 per cent). Morestin, Davis, Brewer, Steiner, Polya and others described extensive plastic operations which included the excision of all of the soft parts of the cheek, as well as a submaxillary dissection. All of these writers emphasized the necessity of wide removal of the soft parts of the cheek. The deformity is great, and ankylosis of the jaws from cicatricial contraction of the cheek is common. To avoid this complication, Morestin and Warren recommended excision of one-half the mandible in all of these cases, and

the former stated that in one case of early cancer of the cheek, the extent of the operation which he performed "provoked a veritable stupor in the assistants and in the patient's own physician." The outcome was, however, successful, and at the time of the report, the patient had been cured of the disease for two years.

In our opinion, the most successful method of treatment of cancer of the cheek is a combination of irradiation and surgical intervention. The treatment of the primary lesion and of the cervical metastases should be considered as separate problems. Irradiation is preferable to surgical treatment for the control of the primary lesion.

Prophylactic neck dissection is not justified. The method of treatment of cervical metastases should be selected to suit the individual patient and may be by surgical means alone, by irradiation alone or by a combination of the two procedures.

SUMMARY

1. An unselected series of ninety-nine cases of cancer of the cheek is subjected to critical analysis.

2. The methods of treatment employed are discussed in detail.

3. The net results at the end of five years show 30 per cent of the patients living and free from disease.

OSTEOGENESIS

AN EXPERIMENTAL STUDY

J. DEWEY BISGARD, M.D.
OMAHA

The genesis of bone, the palimpsest of the evolution of man, remains to this day undetermined and a subject of much controversy. This controversy involves not only the fundamental problems of the chemical processes of ossification but also its histogenesis. Without established knowledge of the rôle (if any) played by tissue cells in the laying down of bone and of the specialization required of cells for such a function, the part played by such tissues as the periosteum, endosteum, cartilage and granulation tissue can only be conjectured. However, I have presented experimental results which indicate that the periosteum is particularly conducive to the deposition of new bone on its cambium surface.

Probably no other problem in histologic physiology has been investigated so extensively and has given rise to more conflicting results. From a review of the literature, it is apparent that much of the conflict and confusion has arisen from the error of making direct comparison of experimental results without adequate appreciation of the wide differences in osteogenic response brought about by the multitudinous minor individual variations in experimental procedure. Among the factors which exert great influence are: (1) the age of the subject, (2) the type of bone (spongy or dense), (3) the nutrition of both the bone and the periosteum (the normal variations in different parts of the body and the changes brought about by experimental procedure), (4) the operative technic used in the handling of the tissues (hemostasis, trauma, etc.), (5) the extent of the stimulus resulting from function and (6) the degree of immobilization. Evidence of the influence exerted by some of these factors has been brought out in my investigation.

METHOD AND MATERIAL

With one exception, young dogs were used for all experiments. One old animal was utilized to demonstrate the influence of the age of the subject on the osteogenic response of the tissues.

All observations were made on the ribs and their cartilages and the costal periosteum and perichondrium, for the following reasons:

1. Each costal arch is a dispensable individual unit which can be removed in its entirety without causing appreciable dysfunction. For

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the same reason and on account of the multiplicity of the ribs, it was possible to utilize each animal for several experiments.

2. The rich blood supply of both the rib and its periosteum and the cancellous structure of the rib provide circumstances optimally favorable to osteogenesis.

3. Continuous respiratory excursions and stresses after operation contribute uninterrupted functional stimuli to osteogenesis.

The operative procedures were carried out with ether anesthesia and with rigid aseptic surgical technic. Although each dog was the subject of several experiments, each procedure was performed independently of the others, through a separate incision, one costal segment always being left undisturbed between the operative sites.

All of the wounds healed by primary intention. The animals were killed from sixty-five to ninety-three days after operation and the hemithoracic walls which were operated on were removed *en masse*; roentgenograms were made, and the individual specimens were removed for gross and microscopic study.

Since each experimental procedure was repeated in two or more dogs, and since more than one experiment was carried out in each animal, each problem and its results will be presented in logical sequence, and a brief protocol for each animal is given in the accompanying table.

THE PERIOSTEUM. IS IT ONLY A LIMITING MEMBRANE?

In each experiment the periosteum was elevated carefully from the rib with a dull instrument in an effort to obtain cleavage which would not detach small fragments of bone with the periosteum. Care was exercised to obtain good hemastasis, to avoid damage to the intercostal blood vessels and nerves and to minimize trauma of the periosteum.

EXPERIMENT 1 (dogs 70, 71 and 72).—*Subperiosteal removal of the entire rib.*

In each of these dogs an entire rib was removed subperiosteally; it was disarticulated from the vertebra posteriorly and from the costal cartilage anteriorly, leaving the periosteum undisturbed except for the excision of a long, narrow strip for use in the control experiment, described subsequently (experiment 9; diagram 1, fig. 1).

Roentgenograms of the specimens obtained eighty-five days after operation are reproduced in figure 2 *D*, 3 *C* and 4 *B*. In each instance a large quantity of new bone was deposited in the periosteal bed, irregularly replacing the original rib. The breaks in continuity shown in figure 4 *B* probably represent fractures of the newly formed rib.

Both grossly and microscopically there was a continuous ribbon of new bone extending from the costal cartilage to within a short distance

of the vertebra. The regenerated rib was thin and irregularly nodular and consisted of segments with normal costal architecture (fig. 5) separated by small segments composed of newly formed cartilage and newly formed bony trabeculae.

EXPERIMENT 2 (dogs 17 G and 18 G).—*Subperiosteal removal of the entire rib and its cartilage.*

To preclude the possibility encountered in the first experiment that the regenerated rib might arise from the costal cartilage the same procedure was repeated in two dogs with the additional resection of the costal cartilages. The rib was disarticulated from its vertebral attachment and with its cartilage was unsheathed and resected to the sternum (diagram 2, fig. 1).

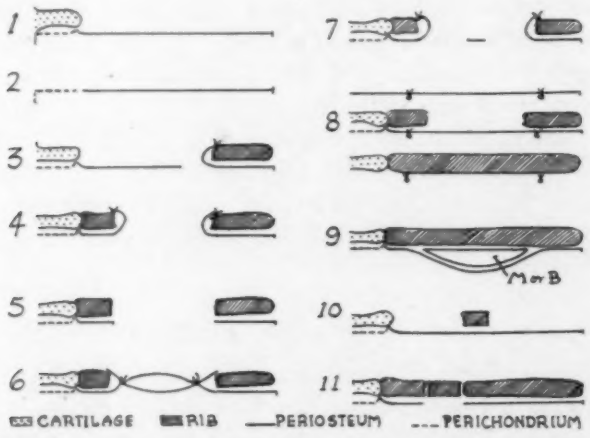

Fig. 1.—Diagrams illustrating the technic of several of the experiments: *1*, experiment 1; *2*, experiment 2; *3*, experiment 3; *4*, experiment 4; *5*, experiment 5; *6*, experiment 6; *7*, experiment 7; *8*, experiment 11; *9*, experiments 13 and 14; *10*, experiment 16, and *11*, experiment 17. *M* or *B* denotes the muscle or the rubber bag interposed between the periosteum and the rib.

A narrow strip of periosteum was resected for use in the control experiment (experiment 9).

Both animals were killed eighty-six days after operation. The postmortem roentgenogram of dog 17 (fig. 6 *A*) shows that the rib regenerated irregularly and incompletely up to but not beyond the periosteoperichondrial junction. From this point to the sternum there is no shadow of greater density than that of soft tissue.

Macroscopically, these regenerated ribs were nodular, irregularly shaped, broader, thinner and more pliable than a normal rib. The perichondrial bed had the consistency and appearance of fascia. Nowhere did it contain tissue with skeletal rigidity.

The microscopic appearance of the regenerated rib was essentially the same as that described in experiment 1. The new bone apparently had developed both by direct and by enchondral osteogenesis. The perichondrium consisted of a layer of dense fibrous tissue several times its original thickness. In it were small scattered nodules of cartilage which, when treated with Mallory's connective tissue stain, proved to be fibrocartilage.

EXPERIMENT 3 (dog 7).—*Subperiosteal resection of the anterior half of the rib with exclusion of the end of the posterior costal stump.*

Fig. 2 (dog 70).—*A* indicates the periosteum only, zenkerized (experiment 15 B); *B*, the interposition of the costal cartilage (experiment 17; fig. 1, diagram 11); *C*, the posterior costal stump sealed with a periosteal flap (experiment 3; fig. 1, diagram 3), and *D*, a subperiosteal excision of the entire rib (experiment 1; fig. 1, diagram 1).

From the posterior portion of the periosteal bed which was left after subperiosteal resection of the anterior half of the rib, a pedicle flap of periosteum was dissected from the pleura and intercostal structures and sutured tightly over the end of the posterior costal stump so as to seal it completely (diagram 3, fig. 1).

A narrow strip of periosteum was removed for the control experiment (experiment 9).

The duration of the experiment was eighty-five days. As illustrated in the roentgenogram (fig. 2 *C*) regeneration occurred along the entire periosteal bed, but in the area from which the periosteal flap had been raised no shadow of bone is discernible.

Microscopic examination verified these roentgenologic findings. The regenerated segment presented a picture similar to that described in experiment 1. The old bone of the severed end of the costal stump for a short distance posteriorly was necrotic and was undergoing

Fig. 3 (dog 71).—*A* indicates the devascularized periosteal bed (experiment 11; fig. 1, diagram 8); *B*, the periosteum, zenkerized (experiment 15 B); *C*, the subperiosteal excision of the entire rib (experiment 1; fig. 1, diagram 1), and *D*, the isolated segment of the periosteum (experiment 6; fig. 1, diagram 6).

absorption and replacement by new bone. Over its surface and between it and the periosteal flap there were considerable newly formed cartilage and bony trabeculi.

EXPERIMENT 4 (dog 72).—*Subperiosteal resection of a costal segment 7 cm. in length; isolation of both ends of the rib with periosteal flaps.*

The periosteal tube between the severed ends of the rib was carefully dissected from the intercostal structures and from the pleura and

divided into two flaps which were turned and sutured tightly over the ends of the costal stumps, so that only pleura formed the floor of the decostalized bed. The procedure is illustrated in diagram 4, figure 1.

A small piece of periosteum was excised for the control experiment (experiment 9).

The roentgenogram (fig. 4 *A*) of the postmortem specimen obtained eighty-three days after operation presents shadows of newly deposited bone covering the severed ends of the rib and complete absence of bone in the space intervening between the costal stumps.

These findings were verified by macroscopic and microscopic observations. The microscopic picture is illustrated in figure 7. The

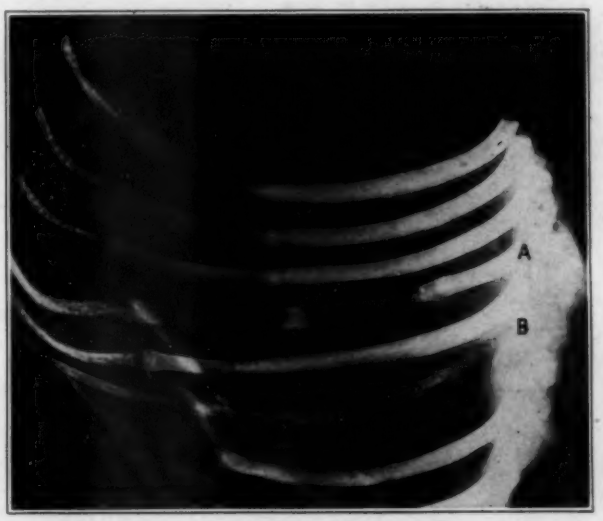

Fig. 4 (dog 72).—*A* indicates the deperiostealized bed; the costal stumps are sealed with periosteal flaps (experiment 4; fig. 1, diagram 4). *B* indicates the subperiosteal resection of the entire rib (experiment 1; fig. 1, diagram 1).

free ends of both ribs contained necrotic old bone which was undergoing transformation; they were covered by a layer of newly formed bone, osteoid tissue and cartilage. This new formation was sharply delimited by the periosteal caps. The space between the costal stumps was bridged by fibrous tissue only.

EXPERIMENT 5 (dogs 78 and 18 G).—*Resection of 7 cm. of both the rib and its periosteum.*

After removal of the costal segment subperiosteally, the periosteum was dissected from the intercostal structures and pleura and was excised so that only pleura formed the floor of the gap between the ends of the rib (diagram 5, fig. 1).

A portion of the excised periosteum was decalcified and sectioned for study in the control experiment (experiment 9).

A roentgenogram of a sixty-seven day specimen (fig. 8 *A*) shows proliferation of new bone about the costal ends, particularly the anterior one, but no evidence of bone in the gap between the stumps.

As in the experiments described earlier, microscopic study revealed necrotic old bone at the free ends of the costal stumps which was undergoing replacement by creeping substitution. They were capped

Fig. 5.—A low power photomicrograph of the regenerated costal segment referred to in experiment 1. Note the reproduction of the normal costal architecture.

by a layer of new bone which closed the open medullary spaces. There was evidence of enchondral osteogenesis. Neither bone nor cartilage was found in the tissue intervening between the costal stumps; only fibrous tissue was present.

EXPERIMENT 6 (dog 71).—*Isolation of a segment of periosteum in its normal bed.*

The ends of the periosteal tube which was left after the subperiosteal resection of a costal segment approximately 7 cm. in length were closed tightly around the ends of the costal stumps with encircling

sutures of heavy silk carefully placed to avoid damaging or including the intercostal vessels. Thus the ends of the rib were sealed, and a segment of periosteum was isolated (diagram 6, fig. 1).

A narrow strip of periosteum was excised for study in the control experiment (experiment 9).

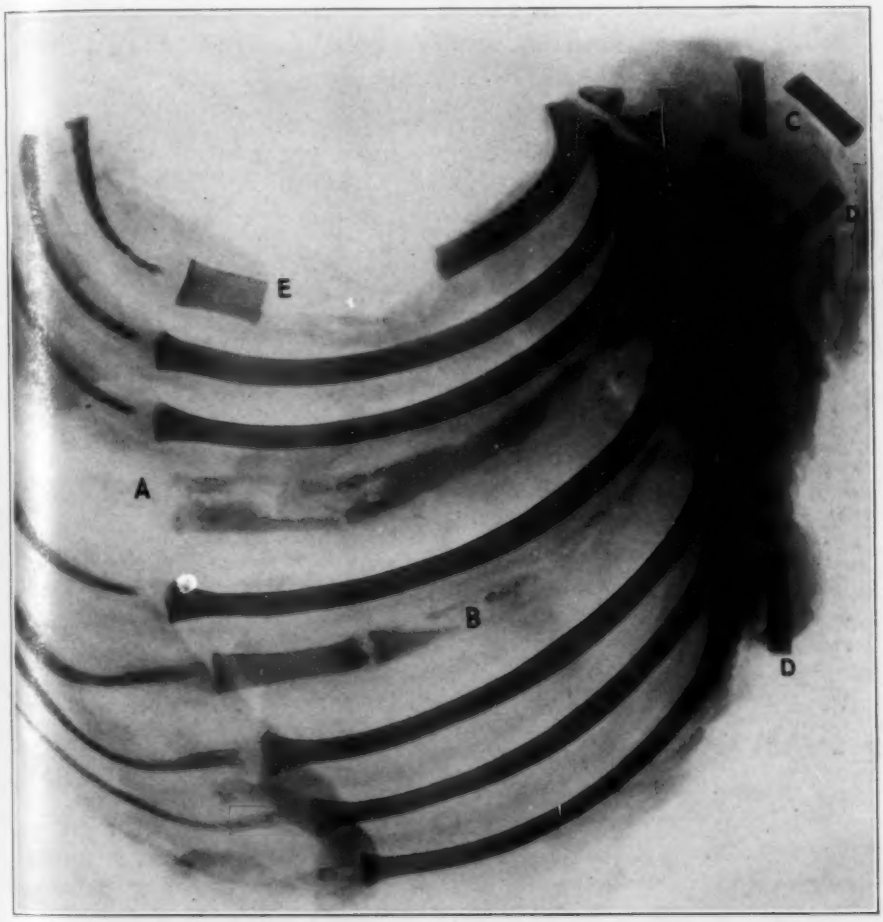

Fig. 6 (dog 17).—*A* indicates the subperiosteal and subperichondrial resection of the entire rib and its cartilage (experiment *2*; fig. 1, diagram 2); *B*, the costal stumps only, zenkerized (experiment 15 A); *C*, the transplanted costal segments (experiment 18 A); *D*, the transplanted zenkerized costal segments (experiment 18 C), and *E*, a costal segment excised post mortem for purposes of comparison with the costal stumps of the experimental specimens (the latter in contrast show rounded edges from absorption and the deposition of new bone).

The result of this experiment eighty-five days after operation is shown in the roentgenogram (fig. 3 *D*). Extensive absorption of the costal ends had taken place, and in the space intervening between and

isolated from the costal stumps there was a well formed segment of bone which corresponded to the isolated segment of the periosteal bed.

On gross examination there were three distinct pieces of bone separated by two white scars which stood out sharply on the inner surface of the periosteum.

Microscopically, the ends of the costal stumps contained necrotic old bone which was invaded by granulation tissue and was undergoing absorption and some newly formed bony trabeculi. On the surface of

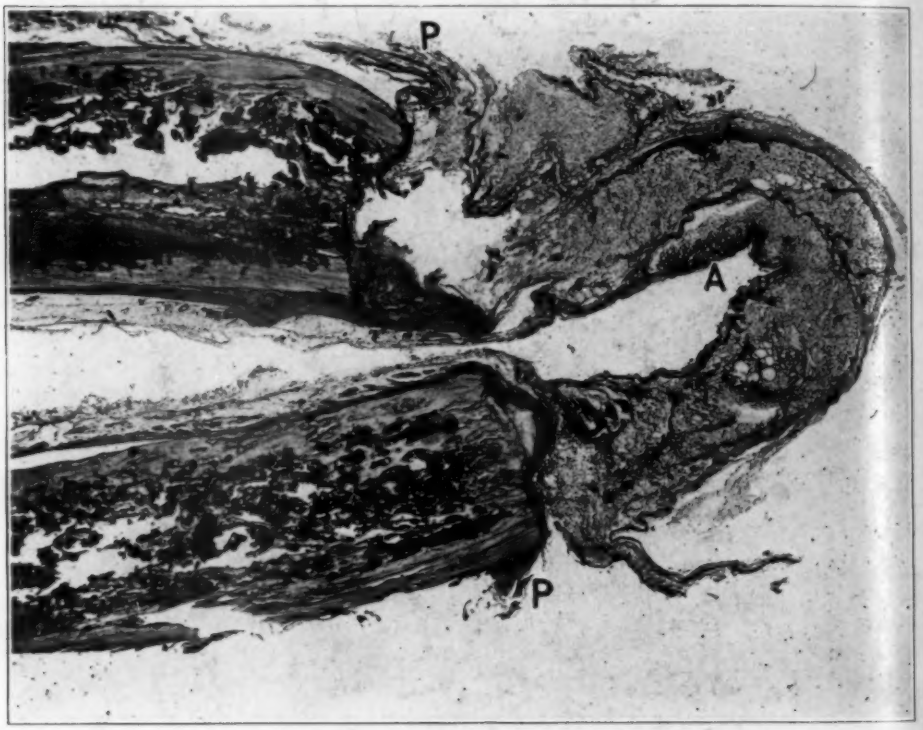

Fig. 7.—A low power photomicrograph (experiment 4; specimen A, fig. 4), showing the costal stumps covered with flaps of periosteum (*P*) turned back from the decostalized bed and sutured tightly over both ends of the rib. The space (*A*) between the costal stumps from which both bone and periosteum have been entirely removed is filled with young fibrous tissue. It contains neither new bone nor cartilage. Note the new bone between the ends of the rib and the periosteum which covers them.

the isolated periosteal segment was a well formed piece of bone. Between it and the ends of the rib there were spaces filled with young fibrous tissue and foci of chronic inflammation with many foreign body giant cells surrounding small bits of silk thread. A photomicrograph of the specimen is shown in the lower illustration of figure 10.

It is probable that the foreign body reaction was responsible for the extensive absorption of the ends of the rib.

EXPERIMENT 7 (dogs 77 and 18 G).—*Isolation of a segment of periosteum.*

After subperiosteal resection of 9 cm. of a rib, a small segment of periosteum in the center of the periosteal bed was left undisturbed, and the remainder of the membrane was raised from the pleura and inter-

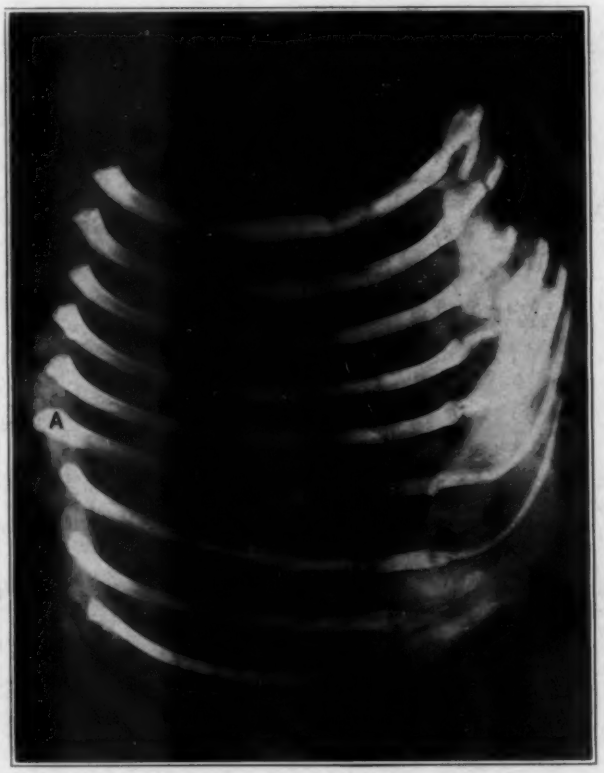

Fig. 8 (dog 78).—*A* indicates a complete resection of both the costal segment and its periosteum (experiment 5; fig. 1, diagram 5).

costal structures and sutured as two pedicle flaps over the ends of the costal stumps in diagram 7, figure 1.

Small pieces of periosteum were also excised for the control experiment (experiment 9). .

In the roentgenogram of the specimen obtained sixty-seven days after operation (fig. 9 C) there is seen an irregular shadow of newly deposited bone in the area occupied by the isolated segment of periosteum.

These findings were substantiated by gross examination.

The ends of the rib were shown by microscopic study to contain necrotic bone and trabeculi of new bone, the latter sealing the exposed cancellous spaces. New bone and cartilage filled the spaces between the ends of the stumps and the periosteum covering them. The space between the two stumps was bridged with a layer of fibrous tissue containing a small island of new bone (fig. 10 *A*).

EXPERIMENT 8 (dogs 70, 77, 78 and 18 G).—*Free transplantation of periosteum.*

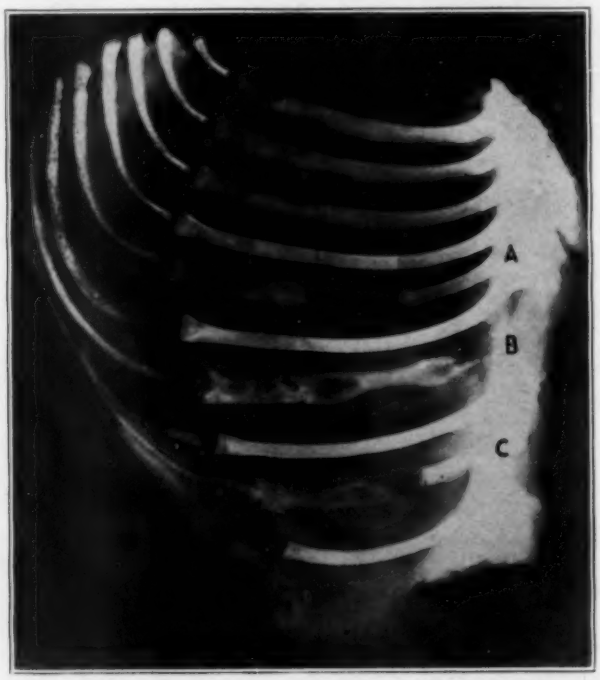

Fig. 9 (dog 77).—*A* indicates both the periosteum and the ends of the rib, zenkerized (experiment 15 C); *B*, a subperiosteal resection of the entire rib except for a small segment (experiment 16; fig. 1, diagram 10), and *C*, an isolated segment of the periosteum, the ends of the costal stumps being sealed with periosteal flaps (experiment 7; fig. 1, diagram 7).

In four young dogs strips of periosteum to which small linen sutures were attached for identification were transplanted to the erector spinae muscles.

At postmortem examination from sixty-seven to eighty-six days later two of the transplants could not be found, but the two which were recovered contained (fig. 11 *a*) small nodules of new bone encapsulated in fibrous tissue. In two or three areas fibers of thread were surrounded by a zone of active inflammation. In neither specimen

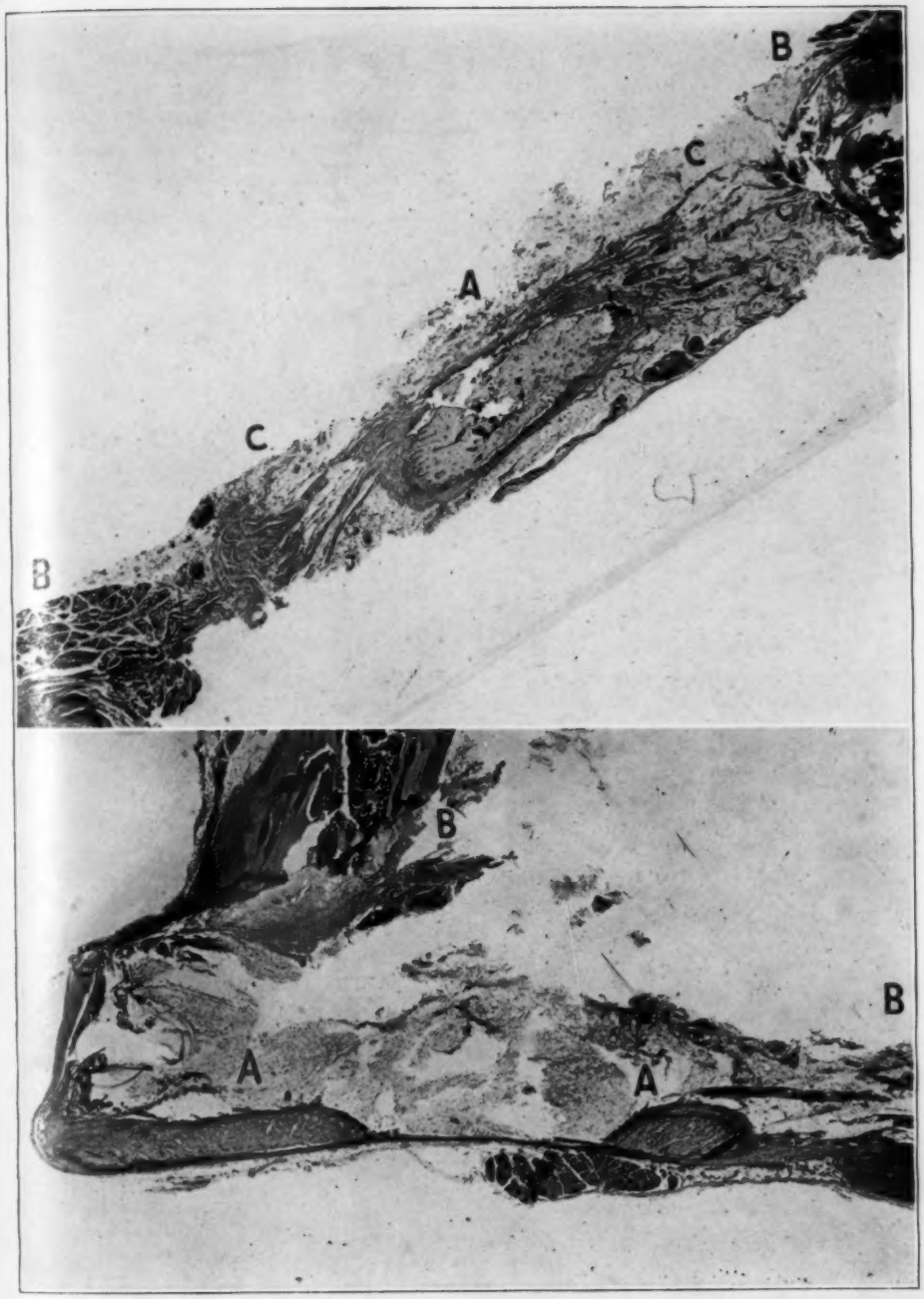

Fig. 10.—The upper illustration is a low power photomicrograph of specimen *C* shown in figure 9 (experiment 7), showing the island of new bone (*A*) which has been deposited on the isolated segment of periosteum between the costal ends (*B*). The two periosteal flaps which were raised from the bed at *C* to isolate the central segment (*A*) can be seen sealing the costal stumps (*B*). Note that the new bone has not extended into the deperiostealized areas (*C*). The technic is shown in figure 1, diagram 7. The lower illustration is the low power photomicrograph of the specimen shown in *D*, figure 3 (experiment 6). Note the islands of new bone (*A*) in the periosteal bed which was isolated from both costal stumps (*B*), with encircling sutures which sealed the ends of the rib. The operative procedure is illustrated in figure 1, diagram 6.

was there old bone or evidence to suggest that fragments of bone had been transplanted with the periosteum. There was no cartilage, and consequently no direct indication of endochondral osteogenesis.

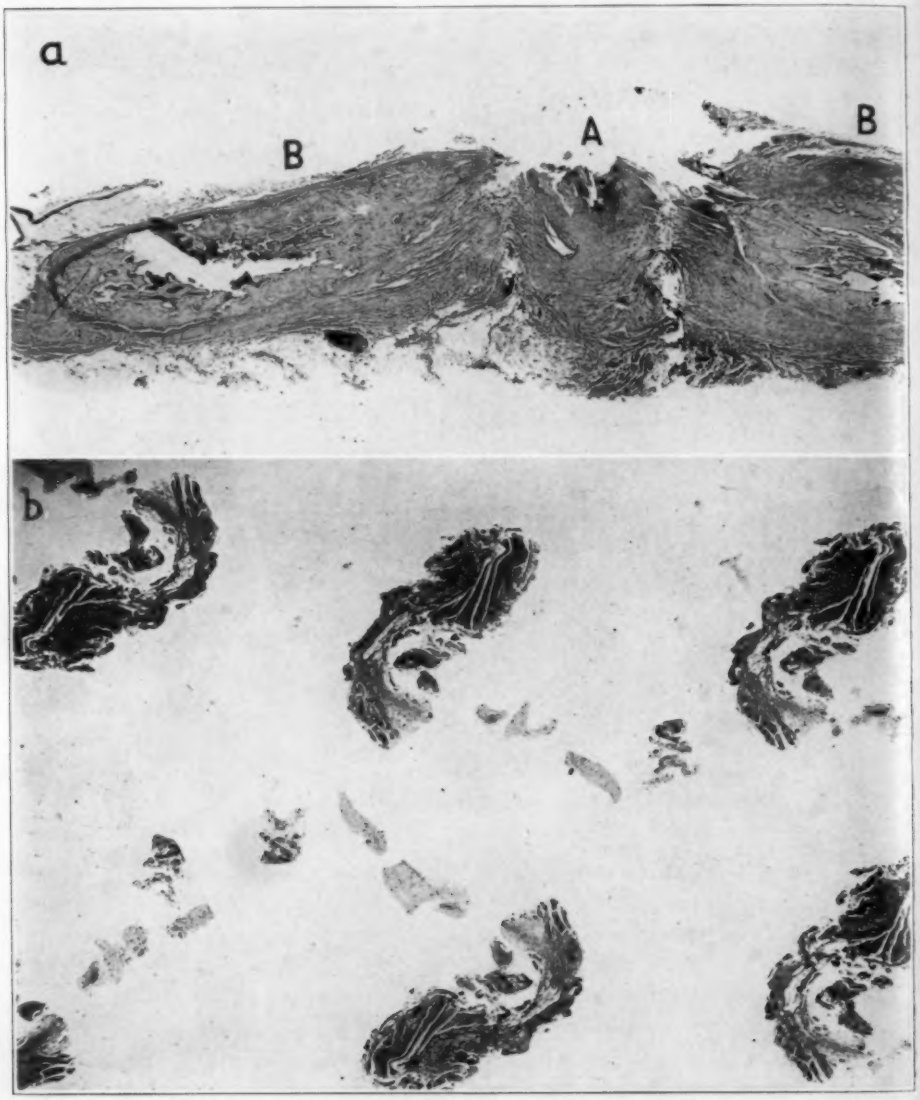

Fig. 11.—In *a* is presented a low power photomicrograph of a specimen removed from dog 77 (experiment 8). In the encapsulated piece of periosteum which had been transplanted to the erector spinae muscles, two nodules of new bone (*B*) were found. The inflammatory tissue (*A*) surrounds fibers of the linen thread suture which were buried with the transplant to aid identification. In *b* are shown serial sections of one of the fresh strips of periosteum used in experiment 9. This illustrates the method of investigating the control material.

EXPERIMENT 9.—*Control.*

Some of the investigators who believe that the periosteum has no specific osteogenic potentialities have suggested that the new bone which is laid down in periosteal beds or on periosteal transplants may arise from small fragments of bone which adhere to and are transplanted with this membrane. In an attempt to test this contention and to obtain as much control data as possible, fourteen narrow strips of periosteum were excised from the periosteal beds of eight animals after subperiosteal resection of the costal segments. These have been noted in experiments 1, 2, 3, 4, 5, 6, 7, 10 and 17. Each strip was decalcified and cut into innumerable serial sections, and many were mounted for study as illustrated in figure 11 *b*. In only one of the fourteen specimens was bone found.

THE INFLUENCE OF CERTAIN FACTORS ON THE OSTEOGENIC RESPONSE OF THE PERIOSTEUM

EXPERIMENT 10 (dog 16 G).—*Influence of age.*

Three of the experiments with young animals reported earlier were repeated in an obviously aged dog.

A. Subperiosteal resection of an entire costal unit, as in experiment 2.

A small strip of the periosteum was removed to be used in experiment 9. The roentgenographic (fig. 12 *B*), gross and microscopic examination of the specimen obtained ninety-three days after operation showed no evidence of costal regeneration. There was no new or old bone or cartilage, the periosteum and perichondrium consisting of thickened pliable bands of dense fibrous tissue. Compare these findings with those reported in experiment 2 and the roentgenogram illustrated in figure 6 *A*.

B. Subperiosteal resection of a costal segment leaving small costal stumps.

In the roentgenogram (fig. 12 *A*) there can be seen no evidence of costal regeneration. The periosteal bed consisted entirely of fibrous tissue. The ends of the rib contained both necrotic bone undergoing absorption and a few trabeculae of new bone on the surface. Compare these results with the roentgenographic and other findings reported in the experiments with young animals.

C. Free transplantation of the periosteum.

Three strips of periosteum were transplanted to the erector spinae muscles with attached linen ligatures for identification. Two of the specimens were recovered at postmortem examination and consisted of firm, fibrous nodules which on section were found to be composed solely of fibrous tissue with an active chronic inflammatory reaction around bits

of thread in a few areas. There was no bone or cartilage. Compare these findings with those reported in experiment 8.

EXPERIMENT 11 (dogs 71 and 18 G).—*Circulatory influence.*

After resecting 7 cm. of a rib subperiosteally in each animal, the intercostal vessels were ligated 2 cm. distal and proximal to the ends

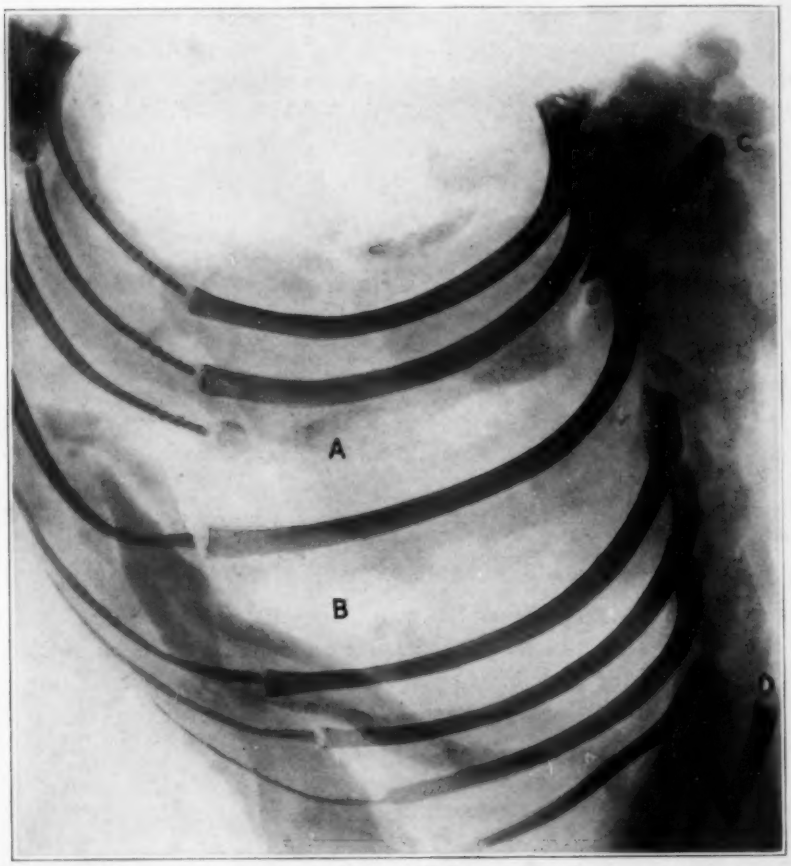

Fig. 12 (dog 16, an aged animal).—*A* indicates a subperiosteal resection of a long costal segment, leaving small stumps; *B*, a subperiosteal and subperichondrial resection of the entire rib and its cartilage. Note in both *A* and *B* complete absence of costal regeneration from the periosteum and costal stumps of this old animal. Compare with similar experiments in young animals shown in the preceding roentgenograms. *C* indicates free costal transplant, and *D*, free zenkerized costal transplants.

of the decostalized bed. In an endeavor to impoverish further the blood supply to the part by interrupting a portion of the collateral circulation, the vessels accompanying the rib above and the one below were ligated at both extremities in the same plane as those of the resected

segment. The principle of the procedure is illustrated in diagram 8, figure 1.

The result eighty-five days after operation is shown in the postmortem roentgenogram of one of the animals (fig. 3 *A*). Apparently no new bone was deposited on this devascularized segment of periosteum.

Microscopically the tissue was entirely fibrous, and there was no trace of bone or cartilage. The ends of the costal stumps contained much necrotic old bone, which was undergoing revascularization and absorption. New bone had been deposited on the surface and in the revascularized spaces.

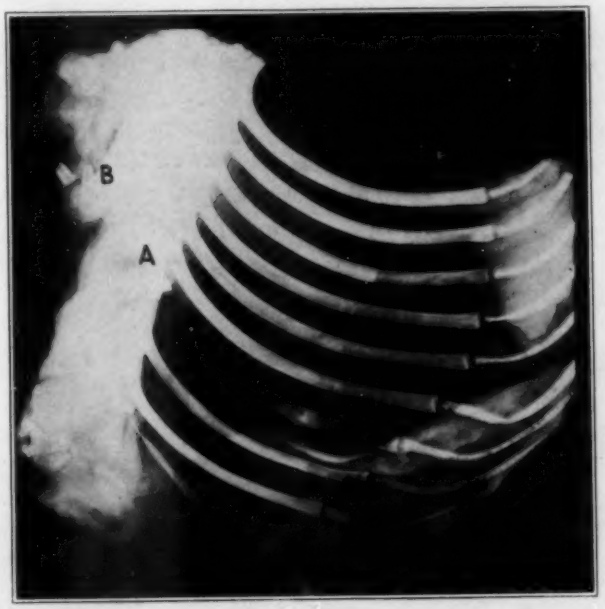

Fig. 13 (dog 80).—*A* indicates the periosteal bed, curetted and rubbed vigorously with gauze. Note that the deposition of new bone extends for a short distance beyond the end of the anterior stump and that the rest of the decostalized bed contains only one small island of bone. *B* indicates free costal transplants in muscle.

EXPERIMENT 12 (dogs 80 and 76).—*Influence of trauma.*

A 9 cm. decostalized periosteal bed was curetted and rubbed vigorously with gauze to remove the cambium layer.

The roentgenogram of one of the specimens sixty-five days after operation is shown in figure 13 *A*. Considerable new bone was deposited for a short distance beyond the end of the anterior costal stump, but throughout the remainder of the periosteal bed there is seen only one small nodule of new bone.

Macroscopic and microscopic examinations were confirmatory. The new bone appeared to arise at least partially by enchondral estrogenesis.

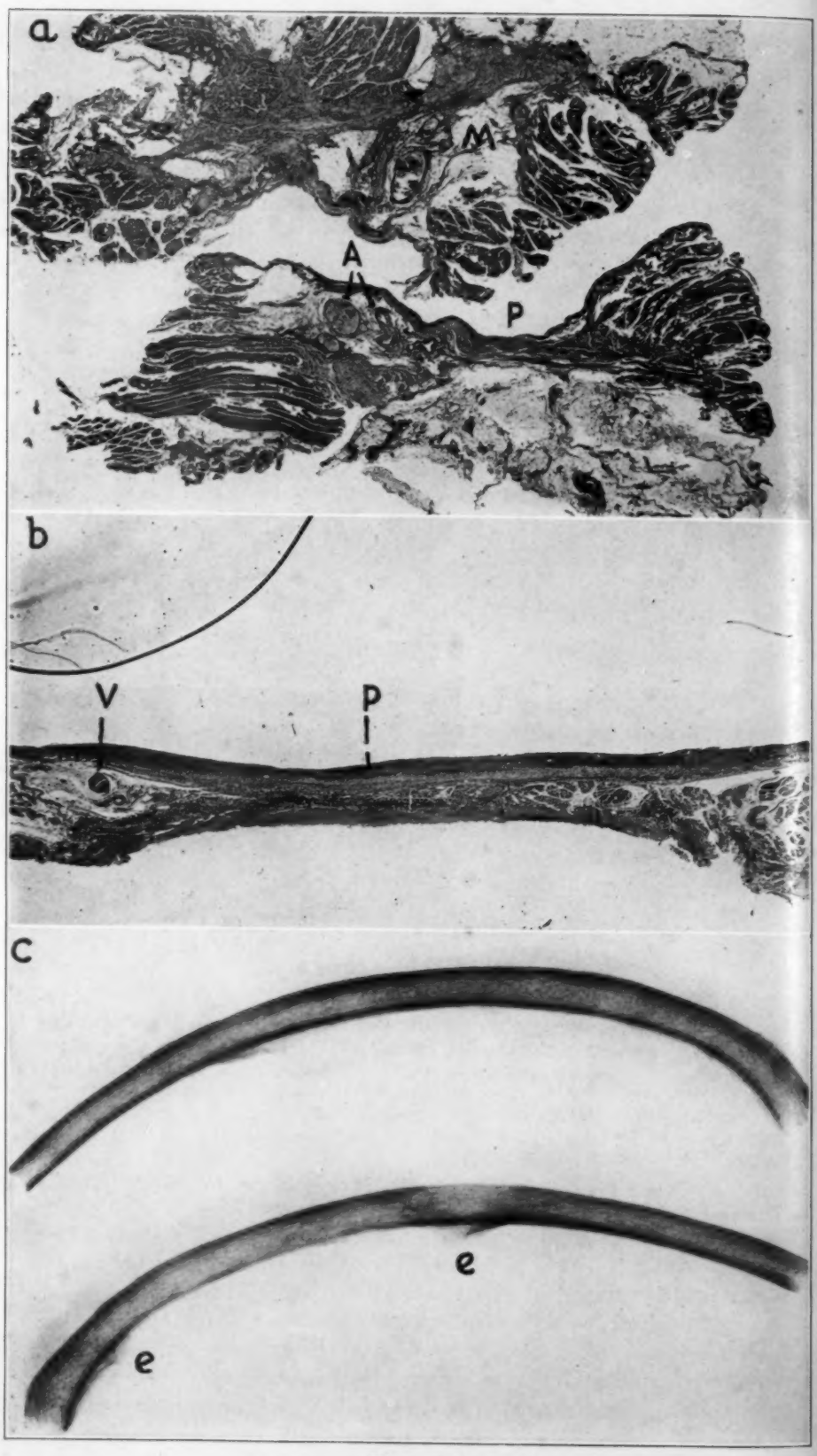

Figure 14

EXPLANATION OF FIGURE 14

Fig. 14.—In *a* (dog 84), is presented a low power photomicrograph of the specimen obtained in experiment 13, showing the pedicled transplant of muscle (*M*) interposed between the rib and its periosteum (*P*). The intercostal vessels and nerve are labeled *A*. Note that no new bone has been deposited on the periosteal surface (*P*). In *b* (dog 81), is presented a low power photomicrograph of a specimen obtained in experiment 14. The inflammation resulting from the rubber bag interposed between the rib and its periosteum has resulted in marked thickening of the periosteum (*P*). The intercostal vessels and nerve are labeled *V*. Note that no new bone has been deposited on the surface of the periosteum. In *c* (dog 84 F), is presented a postmortem roentgenogram of two ribs obtained in experiment 13, showing nodules of new bone (*C*) deposited in the angle between the rib and the periosteum. In the space between these two nodules the periosteum was separated from the rib by the interposed muscle.

EXPERIMENT 13 (dog 84 F).—*Influence of apposition of muscle.*

With a technic similar to that of pneumolysis of the pectoral muscle described by John Alexander,[1] long segments of four contiguous ribs were stripped of their periosteal sheaths, and a muscle flap which had been raised from the thoracic wall and had been fashioned with an adequate vascular pedicle was insinuated between the internal surface of the bare ribs and the mesially displaced periosteum and intercostal bundles. The technic is illustrated in diagram 9, figure 1.

The animal was killed sixty days after operation. As illustrated in figure 14 *a*, no new bone had been deposited on the surface of the periosteum. The contacting muscle was loosely adherent to the periosteum in some areas and densely adherent in others. In the angles between the rib and the periosteum at both borders of the interposed muscle small nodules of bone had been deposited (fig. 14 *c*).

EXPERIMENT 14 (dogs 81 and 82).—*Influence of apposition of foreign body.*

The procedure, a pneumolysis, which has been described in experiment 13, was repeated in two dogs, with the exception that the space between the ribs and the periosteum was filled with a rubber bag instead of muscle. The rubber bag consisted of a surgeon's glove filled with sterile salt solution. Recurring accumulations of serum in the subcostal space bulged the healed incision and necessitated repeated aspirations.

No infection occurred, and the animals were killed sixty-two and sixty-five days after operation. Each bag had become encapsulated by a thick layer of fibrinous exudate.

Microscopic examination revealed that the denuded ribs were entirely necrotic, and that the periosteum and pleura (fig. 14 *b*) were markedly thickened and presented an active inflammatory reaction. Nowhere on the surface of this inflammatory membrane could bone be palpated, and none was found in the sections studied.

EXPERIMENT 15.—*Influence of chemical cauterization.*

A. (dogs 76 and 17 G).—*Costal stumps only treated with Zenker's solution, the periosteum being carefully guarded from contact with the solution.*

The roentgenogram of one of the specimens (fig. 6 *B*) obtained eighty-six days after operation indicates that new bone was irregularly deposited in the periosteal bed.

On palpation the segment was semirigid throughout and contained scattered hard nodules.

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1. Alexander, John: Supraperiosteal and Subcostal Pneumolysis with Filling of Pectoral Muscle, Arch. Surg. **28**:538 (March) 1934.

Microscopically the ends of both the costal stumps were necrotic and contained no new bone. In the decostalized bed there were segments of new bone with well formed costal architecture and nodules containing cartilage, bony trabeculae and osteoid tissue.

B. (dogs 70 and 71).—*Periosteum only treated with Zenker's solution.*

This experiment repeated the procedure of 13 *A*, with the exception that only the periosteum was treated with Zenker's solution. The ends of the rib were covered with bone wax while the solution was being applied to the periosteal bed.

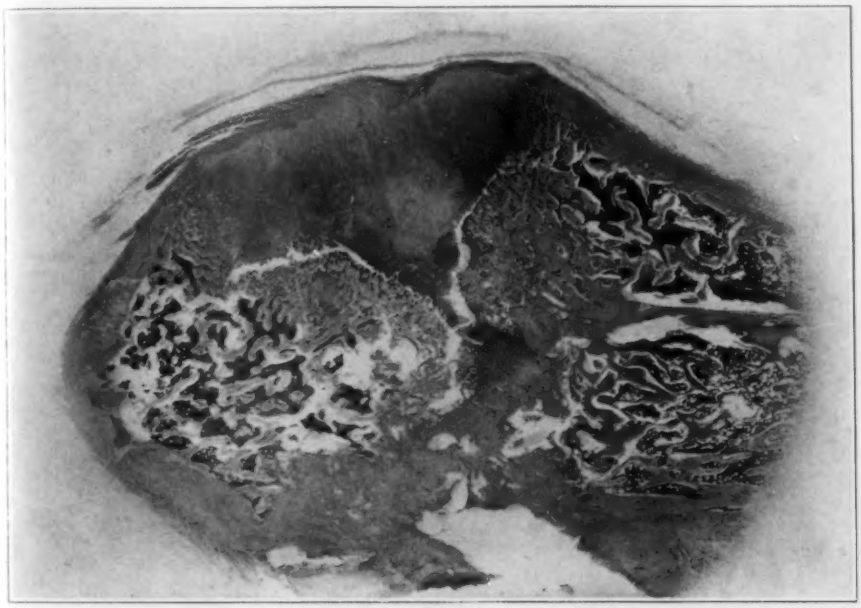

Fig. 15 (dog 70).—A low power photomicrograph of specimen *B* shown in figure 2 (experiment 17). New bone proliferating from the ends of the costal stumps has invaded and replaced much of the interposed segment of cartilage and has established bony union. Note the marked density of some of the new bone. The experimental operative technic is illustrated in figure 1, diagram 11.

The roentgenograms (figs. 2 *A* and 3 *B*) of the specimens obtained sixty-five days after operation show no evidence of bone in the zenkerized periosteal beds.

Neither cartilage nor bone was found on microscopic examination. The tissue was entirely fibrous. The ends of the rib contained both old dead bone and newly formed bone and cartilage, some of the new bone apparently arising by enchondral osteogenesis.

C. (dogs 77 and 76).—*Both the periosteum and the costal stumps treated with Zenker's solution.*

The operative procedure differed from that of experiments 13 *A* and 13 *B* only in respect to the application of Zenker's solution to both the periosteum and the ends of the costal stumps.

As indicated in one of the roentgenograms (fig. 9 *A*), no new bone was found in the zenkerized periosteal bed, and only a small amount was deposited on the surface of the ends of the rib. The old bone of the ends of these stumps was entirely necrotic.

ENDOSTEAL AND OSTEAL OSTEOGENESIS

EXPERIMENT 16 (dog 77).—*Costal regeneration aided by the presence of a segment of rib.*

An entire rib was resected subperiosteally except for a 3 cm. segment which was left undisturbed in the middle of the periosteal bed (diagram 10, fig. 1). The segments which were resected were disarticulated from the vertebra posteriorly and from the costal cartilages anteriorly.

The roentgenogram of the postmortem specimen (fig. 9 *B*), obtained sixty-seven days after operation, shows that the costal regeneration greatly exceeded that obtained in the experiments in which the periosteum was completely decostalized. The limiting effect of the periosteum is strikingly shown.

Viewed microscopically, the new bone presented normal costal architecture with here and there small nodules of cartilage undergoing ossification. The segment of old bone contained both old dead and living bone. The necrotic portions were extensively invaded and were undergoing transformation.

EXPERIMENT 17 (dogs 70 and 76).—*Costal regeneration from costal stumps.*

In each of two dogs a segment of rib 2.5 cm. in length, and with it its periosteum, was resected. Into this space was fitted snugly a segment of costal cartilage which had been removed from the opposite side of the chest. The cartilage not only bridged the gap and made firm contact with the ends of the rib but rested directly on the pleura, the periosteum having been excised (diagram 11, fig. 1).

A portion of the periosteum was used in the control experiment (experiment 9).

The result of the experiment eighty-five days after operation is clearly shown in the roentgenogram (fig. 2 *B*). Extensive proliferation of new bone occurred at the ends of both costal stumps, presenting the picture commonly seen clinically in pseudo-arthrosis. Similarly, the flared ends cast shadows of the density of osteosclerosis. However, a narrow bridge of bone can be seen traversing the center of the cartilaginous graft to establish union between the costal stumps.

On gross examination there were a nodular fusiform enlargement at the site of the operation and firm union between the costal segments.

The microscopic appearance of a longitudinal section of this specimen is illustrated in figure 15. The new bone at the ends of the rib was large and unusually dense; it invaded the cartilage irregularly. Through the center of the cartilage there was a continuous core of new bone, and the cartilage appeared to be both old and new. The ends of the rib contained some necrotic old bone.

EXPERIMENT 18.—*Free transplantation of costal segments.*

A. (dogs 77, 78, 17, 80 and 16 G).—*Bone only.*

Eight costal segments from 2 to 3 cm. in length were transplanted to the erector spinae muscles and were recovered at postmortem examinations from sixty-seven to ninety-three days after operation. Some of the grafts which appear in the roentgenograms are illustrated in figures 6 *C* and 13 *B*.

All specimens were loosely encapsulated in fibrous tissue and were necrotic in appearance.

Microscopically, five of the transplants appeared to be entirely necrotic, while in the remaining three a few living bone cells near the surface were seen. For a considerable distance from the surface in all specimens the cancellous spaces and haversian canals contained granulation tissue, and the bone in apposition was undergoing absorption. In these areas and along the cortical surfaces there were small excavated indentations, many of which contained giant cells. In all specimens but one there were trabeculae of new bone about the cut ends of the grafts and in the revascularized areas where resorption had taken place. In two, a small amount of new bone had been deposited on the cortical surface, and in no transplant was cartilage seen.

No new bone could be found in one of the two grafts from the old dog (dog 16).

B. (dogs 78 and 80).—*Bone with attached periosteum.*

This experiment differed from the one described in the preceding paragraph in respect to the use of osteoperiosteal grafts. They were removed with strips of periosteum remaining attached to their external surfaces.

Similarly, these transplants appeared to be necrotic and were encapsulated in dense fibrous tissue.

In microscopic section there were definitely more evidence of absorption and larger deposits of new bone, particularly on the cortical surfaces, which presumably were the ones covered with periosteum. Extending out from these surfaces there were areas richly supplied with osteoblasts.

C (dogs 80, 16 G and 17 G).—*Bone treated with Zenker's solution.*

Small segments of seven ribs, some with and some without attached periosteum were soaked for a few seconds in Zenker's solution and immediately buried in the erector spinae muscles.

At the autopsies, from sixty-five to ninety-three days after operation, the segments were removed for microscopic study; all presented the appearance of necrotic bone and encapsulation with fibrous tissue. Some of the grafts are shown in the roentgenogram (fig. 6 *D*).

In microscopic section the bone of all of the specimens was entirely necrotic, and nowhere was there newly formed bone. The cancellous spaces were extensively invaded by young vascular fibrous tissue, and it appeared that considerable absorption of the old bone had taken place.

Description of Dogs

Dog	Description	Weight, Kg.	Date of Operation	Date of Autopsy	Experiments
70	Large young brown female..	22	5/18/32	8/12/32	15B, 17, 8, 9, 3, 1
71	Large young brown male....	23.5	5/18/32	8/12/32	11, 15B, 1, 6, 9
72	Large police pup.....	20	5/20/32	8/12/32	4, 1, 9
76	Young mongrel collie.....	19	6/ 7/32	8/29/32	12, 15A, 15C, 17, 9
77	Large mongrel pup.....	21	6/ 9/32	8/15/32	15C, 16, 7, 8, 18A, 9
78	Young mongrel police.....	24.5	6/ 9/32	8/15/32	5, 8, 18A, 18B, 9
80	Young spitz.....	18	6/11/32	8/15/32	12, 18A, 18B, 18C
16G	Aged mongrel collie.....	27	9/15/32	12/18/32	10A, 10B, 10C, 18A, 18C, 9
17G	Mongrel police pup.....	18	9/21/32	12/18/32	2, 15A, 18A, 18C, 9
18G	Young spaniel mongrel.....	17	9/ 2/32	12/18/32	11, 7, 2, 5, 8, 9
81	Mongrel fox terrier pup.....	14.5	9/10/32	11/12/32	14
82	Young police.....	20	9/12/32	11/16/32	14
84F	Mongrel pup.....	18.5	9/12/32	11/12/32	13

COMMENT

No attempt will be made to review the voluminous literature dealing with the relation of the periosteum to osteogenesis. It is sufficient to note that no truly significant contributions have been made to the early observations and opinions of Duhamel [2] and Ollier [3] that the periosteum has an osteogenic function and to the contradictory experimental results and observations of Macewen [4] expressed in the often quoted words: "While not underestimating the periosteum as a limiting and protecting membrane . . . there are no data to indicate that it can of itself secrete or reproduce bone. It has no osteogenic function."

2. Duhamel du Monceau, H. L.: On the Formation of Bones in Animals and of Wood in Trees, Rec. période. d'obs. de méd., de chir. et pharm. **7**:161, 1757.

3. Ollier, M. L.: Artificial Production of Bone by Displacement and Transplantation of Periosteum, Compt. rend. Acad. d. sc. **47**:905, 1858.

4. Macewen, W.: The Growth of Bone, Glasgow, James Maclehose and Sons, 1912.

These controversial opinions still prevail. While Leriche and Policard,[5] Gallie and Robertson,[6] Cohn and Mann,[7] Murray,[8] Davis,[9] Hunnicut[10] and others have presented important evidence in support of Macewen's views, equally impressive data subscribing to the osteogenic theory of Ollier have been recorded by a large group of investigators, among whom may be mentioned Mayer and Wehner,[11] Axhausen,[12] Lexer,[13] Phemister,[14] Martin,[15] Simon,[16] Rohde,[17] Tomita,[18] Fragenheim,[19] Kropveld,[20] Rollo,[21] Imbert and Jourdan,[22] Polacco,[23]

5. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone, translated by Sherwood Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

6. Gallie, W. E., and Robertson, D. E.: The Repair of Bone, Brit. J. Surg. **7**:211, 1919.

7. Cohn, I., and Mann, G.: Further Study of Bone Repair, South. M. J. **9**:235, 1916.

8. Murray, C. R.: The Repair of Fractures, Minnesota Med. **13**:137, 1930.

9. Davis, quoted by Wirtz: Periosteal Ossification, Arch. f. orthop. u. Unfall.-Chir. **18**:559, 1920-1921.

10. Hunnicut, quoted by Wirtz.[9]

11. Mayer, L., and Wehner, E.: The Significance of the Individual Components of the Bony Tissue in Regeneration and Transplantation of Bones, Arch. f. klin. Chir. **103**:732, 1914.

12. Axhausen, G.: The Histological and Clinical Laws of Free Osteoplasia, Arch. f. klin. Chir. **88**:23, 1908.

13. Lexer, E.: Enderfolge der freien Knochentransplantation, München. med. Wchnschr. **66**:1275, 1919.

14. Phemister, D. B.: The Fate of Transplanted Bone and the Regenerative Power of Its Various Constituents, Surg., Gynec. & Obst. **19**:303, 1914.

15. Martin, B.: Bone Regeneration from the Periosteum, Arch. f. klin. Chir. **120**:744, 1922; Regeneration of Long Bones, ibid. **113**:1, 1919.

16. Simon, R.: On the Outcome of Bone Grafts and the Conclusions Which Can Be Drawn with Regard to the Choice of Material, Gaz. med. de Strasbourg **80**:404, 1922.

17. Rohde, C.: The Course of Regenerative Processes in Long Bones, Arch. f. klin. Chir. **123**:530, 1923.

18. Tomita, C.: Experimental Study of Transplantation of Bone, Virchows Arch. f. path. Anat. **191**:80, 1908.

19. Fragenheim, P.: Permanent Results of Osteoplasty in the Animal Experiment, Arch. f. klin. Chir. **93**:191, 1910.

20. Kropveld, S. M.: Experimental Contributions to the Question of Bone Transplantation, Nederl. maandschr. v. geneesk. **10**:684, 1921.

21. Rollo, S.: Periosteum, Connective Tissue and Calcium Salts in Relation to Osteogenesis, Rev. di biol. **12**:27, 1930.

22. Imbert and Jourdan, R.: Evolution of Osseous Tissue in Osteo-Periosteal Grafts, Compt. rend. Soc. de biol. **82**:115, 1919.

23. Polacco, E.: Comparative Research Work on Graftings of Periosteum and of Young Bone, Arch. per le sc. med. **53**:476, 1929.

Schepelmann,[24] Tricini.[25] Nakahara and Dilger,[26] Jokoi,[27] Berthier,[28] Baschkirzen,[29] Hintzche,[30] Petrow,[31] Lazzarini,[32] Riess,[33] Vogel,[34] Willich,[35] Partsch,[36] Seifert,[37] Hass,[38] Blaisdell,[39] Blaisdell and Cowan,[40] Berg and Thalheimer,[41] Mock,[42] Ham [43] and Haldeman.[44]

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24. Schepelmann, E.: Free Transplantation of Periosteum, Arch. f. klin. Chir. **101**:499, 1913.

25. Tricini, W.: Experimental Contributions to the Study of Periosteal Transplantation, Ztschr. f. orthop. Chir. **30**:69, 1912.

26. Nakahara, T., and Dilger, A.: Subcutaneous and Intramuscular New Formation of Bone by Injection or Implantation of Periosteal Emulsions, Beitr. z. klin. Chir. **63**:235, 1909.

27. Jokoi, T.: Experimental Contribution to the New Formation of Bone by Means of Injection or Implantation of Periosteal Emulsions, Deutsche Ztschr. f. Chir. **18**:433, 1912.

28. Berthier, A.: Histological and Experimental Studies on Muscular Osteoma, Arch. de méd. exper. et d'anat. path. **4**:601, 1894.

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34. Vogel, K.: The Question of Osteoplastic Activity of the Periosteum, Zentralbl. f. Chir. **43**:794, 1916.

35. Willich, C. T.: Experiments in Bone Regeneration and Formation of Pseudoarthroses, Arch. f. klin. Chir. **129**:203, 1924.

36. Partsch, F.: Studies of Bone Regeneration, Deutsche Ztschr. f. Chir. **187**:145, 1924.

37. Seifert, E.: Periosteum and Endosteum in Osteogenesis, Arch. f. Orthop. **17**:329, 1920.

38. Hass, S. L.: Regeneration of Bone from Periosteum, Surg., Gynec. & Obst. **17**:164, 1913.

39. Blaisdell, F. E.: The Osteogenic Function of the Periosteum, Arch. Surg. **11**:933 (Dec.) 1925.

40. Blaisdell, F. E., and Cowan, J. F.: Healing of Simple Fractures, Arch. Surg. **12**:619 (March) 1926.

41. Berg, A. A., and Thalheimer, W.: Regeneration of Bone, Ann. Surg. **67**:331 (March) 1918.

42. Mock, H. E.: Periosteal Transplants in Repair of Delayed Union, Surg., Gynec. & Obst. **46**:641, 1928.

43. Ham, A. W.: A Histological Study of the Early Phases of Bone Repair, J. Bone & Joint Surg. **12**:827, 1930.

44. Haldeman, K. O.: The Rôle of the Periosteum in the Healing of Fractures: Experimental Study, Arch. Surg. **24**:440 (March) 1932.

CONCLUSIONS

1. The costal periosteum is directly or indirectly osteogenic. In young dogs, new bone was constantly deposited on the cambium surface of the periosteum, but in no instance was bone laid down on the dechondralized surface of the perichondrium. Although both membranes, the periosteum and the perichondrium, are composed of fibrous tissue, the periosteum has the important additional inner, richly cellular layer which has been designated by the terms cambium (Billroth [45]), osteogenic (Ollier [45]), proliferative (Virchow [45]) and osteoblastic (Stretzloff [45]). Stripped of this layer of cells (experiment 12), the periosteum apparently was deprived of its osteogenic function and was no more conducive to the formation of new bone than was the dechondralized perichondrium. Nakahara and Dilger [26] succeeded experimentally in obtaining proliferation of new bone from transplanted emulsions of scrapings of the periosteum; these emulsions presumably were composed principally of cells of the cambium layer.

Gallie and Robertson [6] have presented experiments indicating that costal regeneration results entirely from proliferation from the costal stumps. They obtained no regeneration in experiments in which these stumps were tightly sealed from the periosteal beds. Similar experiments carried out by Mayer and Wehner [11] and me yielded results which were absolutely contradictory, as were the results of my experiments in which complete reformation of the ribs took place in the totally decostalized periosteal beds where there were no costal stumps from which proliferation could take place. To exclude the cartilaginous stumps as a possible source for the new bone, both the rib and its cartilage were totally extirpated, and, as shown in experiment 2, complete reformation of the ribs occurred.

Always there exists the probability, as Martin [15] has definitely pointed out, that microscopic fragments of bone remained attached to the periosteum and that these fragments gave rise to the newly formed bone. Obviously a conclusive investigation of this problem is impossible. However, the negative findings in thirteen of the fourteen fresh strips of periosteum which were studied in experiment 9 are at least indicative that residual fragments are not present in large quantities. It is also significant that in the experiments in which periosteum was transplanted and in those in which ribs regenerated in periosteal beds, no old bone or evidence of residual fragments was found. It is unlikely that absorption of old bone would have been so complete that no vestige remained.

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45. Quoted by Riess.[83]

The author has shown in a previous publication [46] that large fragments of a rib, when transplanted into a dechondralized perichondrial bed, establish union with each other and with the sternum and rib, thereby forming a continuous piece of bone with typical costal architecture. The new bone, however, appeared to arise entirely within and from the transplants, and the perichondrium provided merely a protective vascular membrane which aided proliferation. The analogy might be applied to the decostalized periosteum and the possible adherent fragments of bone. This deduction, however, seems inapplicable when one compares the quantitative osteogenic response in the two groups of experiments. The decostalized periosteum containing at most microscopically minute fragments of bone gave rise to an infinitely more rapid and luxuriant growth of new bone than did the large costal grafts in the perichondrial bed.

2. Costal regeneration is limited by the periosteum and fails in the absence of the periosteum. When this membrane was removed from the space between the costal stumps, the newly formed bone merely sealed the open cancellous spaces at the ends of the rib and did not proliferate beyond the cut edge of the periosteum.

Sauerbruch [47] has reported contradictory clinical observations. He cited the case of a patient in whom costal regeneration took place after both the ribs and the periosteum had been removed.

In experiment 17, new bone did proliferate beyond the limits of the periosteum, but the proliferation traversed the center of a transplanted segment of cartilage. It is possible that the cartilage, besides providing an ossifiable medium, maintained a space between the ends of the rib into which new bone could proliferate without interference from scar tissue.

It is interesting that for a short distance the ends of the costal stumps in each experiment became necrotic except for surviving cells along the surfaces and at the borders of vascular spaces.

For some reason which is not apparent, much more new bone was deposited in each instance about the end of the anterior than about the end of the posterior stump.

3. Reparative osteogenesis is influenced by various factors. Age normally exerts an influence which is physiologic. It is a well established fact that the younger the subject, man or animal, the more active are all of the reparative processes of the body tissues. This is particularly true of reparative osteogenesis and has been stressed by the clinical and experimental observations of Ollier,[8] Martin,[15] Lexer,[13]

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46. Bisgard, J. D.: Experimental Studies of Reparative Costal Chondrogenesis and of Transplanted Bone, Surg., Gynec. & Obst. **58**:817 (May) 1934.

47. Sauerbruch, F.: Tr. Surg. Cong., Berlin, 1921; quoted by Martin.[15]

Axhausen,[12] Riess [33] and many others. Riess found that new bone was deposited in all periosteal transplants in dogs less than 9 months of age, and no new bone was found in transplants in older animals. The influence of age is shown strikingly in the comparison of experiment 10 and the accompanying illustration (fig. 12) with the similar experiments and illustrations for the younger dogs.

The influence of the blood supply as a factor in osteogenesis is also well recognized but not thoroughly appreciated. In the rich blood supply of the periosteum Simon,[16] Seiffert [37] and others found the principal source of its osteogenic function. As a result of the interruption of much of its blood supply, the periosteum in experiment 11 gave rise to no new bone. The author has observed the exact clinical counterpart in thoracic operations which necessitated the ligation of several pairs of intercostal blood vessels.

Experiments 13 and 14 indicated that the deposition of new bone by the periosteum is prevented by firm and intimate contact with muscle or with a foreign body such as a rubber bag. I had the opportunity to observe the same result in a patient with pulmonary tuberculosis in whom a rubber bag had been used in an extrapleural pneumolysis to compress the lung and the extrapleural tissues, the latter including the periosteum. Contradictory experimental results, however, were obtained by Oughterson and Harvey.[48] In their animals, costal regeneration took place in the periosteal beds despite the contact of rubber bags. The newly formed ribs are clearly shown in their illustrative roentgenograms. In their experiments the bags were filled with air; when recovered at autopsy they were much smaller, as a result of deflation. They also found it unnecessary to aspirate fluid from the wounds. This discrepancy in experimental results shows the far-reaching influence on osteogenesis of small variations in experimental procedure. It is probable that in my experiments the periosteum was constantly subjected to firmer contact with the foreign body. Trauma which probably removed no more than the cambium layer was sufficient to prevent reparative osteogenesis in experiment 12.

Thermal cauterization and chemical electrical coagulation may either merely retard or entirely prevent reparative osteogenesis, depending on the extent and the degree of destruction produced by these agents. Goeldel [49] and Klapp [50] reported in 1921 that no costal regenera-

48. Oughterson, A. W., and Harvey, S. C.: Localized Collapse of the Lung by Means of an Extrapleural Balloon, Yale J. Biol. & Med. **3**:139 (Dec.) 1930.

49. Goeldel, V.: Ueber Versuche die Knochenregenerationsfähigkeit des Rippenperiostes nach Rippenresektion zu verhüten, Inaug. Dissert., Berlin, 1911.

50. Klapp, R.: Dekompression Operationen am Thorax, Verhandl. d. deutsche Gesellsch. f. Chir. **40**:202, 1911.

tion took place from periosteum which had been seared with the thermal cautery. Klapp also prevented regeneration by the application of nitric acid. Bircher and Kuettner [51] used phenol. Meiss [52] obtained the same result with less destructive chemical solutions. He used zinc chloride and a dilute solution of formaldehyde U.S.P. (1:10) in some experiments, chromic acid in others and Zenker's solution in still others. Head [53] obtained the same results from the use of chromic acid and Zenker's solution and added silver nitrate to the list. Torroca [54] prevented regeneration in the animals in which he used the thermocautery, phenol, a dilute solution of formaldehyde U.S.P. (1:10) and Baum's liquid. The application of pure silver nitrate and of alcohol retarded but did not prevent the formation of new bone. Van Allen [55] has reported that the application of a dilute solution of formaldehyde U.S.P. (1:10) in a series of cases delayed but did not prevent costal regeneration.

In my experiments, no new bone was found in the periosteal beds which had been treated thoroughly with Zenker's solution. Regeneration progressed normally from the periosteum when only the ends of the rib were zenkerized, but there was definite retardation of absorption of old bone and of proliferation of new bone at the ends of the costal stumps. Transplanted zenkerized costal segments had the appearance of encapsulated foreign bodies. They were entirely necrotic and formed no new bone but were considerably invaded by granulation tissue. In contrast, the untreated transplants, also necrotic, were extensively invaded by granulation tissue, were rapidly undergoing absorption and had given rise to some new bone. Much more new bone was present in the grafts covered with periosteum and on the cortical surfaces, which presumably had a covering of periosteum.

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51. Bircher and Kuettner, quoted by Torroca.

52. Meiss, W. C.: Experimenteller Beitrag zur Vereinfachung der Thorakoplastic in mehreren Tempi, Zentralbl. f. Chir. **6**:349, 1930.

53. Head, J. R.: Prevention of the Regeneration of the Ribs, Arch. Surg. **14**:1209 (June) 1927.

54. Torroca, L.: Ricerche sperimentali sui mezzi atti ad impedire la regenerazione ossea dopo l'asportazione sottoperiostea delle costole, Clin. chir. **6**:1433, 1930.

55. Van Allen, C. M.: Chemical Treatment of the Periosteum, Ann. Surg. **97**:368 (March) 1933.

FABELLA (SESAMOID IN THE LATERAL HEAD OF THE GASTROCNEMIUS)

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The sesamoid bone known as the fabella—which literally means "little bean"—is found inconstantly in man on the anterior gliding surface of the external head of the gastrocnemius muscle. Rarely, a sesamoid is seen on the medial head of the gastrocnemius muscle. The inconstancy of the fabella in man and of its location about the knee joint, as evidenced by roentgenographic examination, may be misleading in the diagnosis of conditions of the knee joint (fig. 1 *A*). In rats, cats, rabbits and other animals sesamoids are constantly present [1a] both in the lateral and in the medial heads of the gastrocnemius muscles (figs. 2 *A*, and 3). In these animals one or two additional ossicles are present on the popliteus muscle facing the posterior surface of the tibia.

Sesamoids—for example, those on the lateral or medial heads of the gastrocnemius muscles—are each derived from a specific anlage. The fabellae are not dependent on the activity of the knee joint for their occurrence. Gruber [1b] found that fabellae first appeared as cartilaginous islands at the age of 10. At 17 years of age a center of ossification was apparent in the cartilaginous sesamoid. The fabella, except at the site for the articular cartilage, is attached by Sharpley's fibers to the tendon of the gastrocnemius muscle and to the posterior ligament of the knee joint. The sesamoid is cancellous in structure.

The fabellae, usually bilateral, are located from one-half to one and a half inches (1.27 to 3.77 cm.) above the proximal tip of the fibula when the knee is flexed at an angle of from 150 to 160 degrees. Occasionally the sesamoid can be visualized roentgenographically at the level of the knee joint. Their location may be lateral, posterior or medial to the external femoral condyle. Normally, the ossicles on the lateral head of the gastrocnemius muscle appear to be in close proximity to the posterior surface of the external femoral condyle. As there is a

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1. (*a*) Pfitzner, W.: Beiträge zur Kenntnis des menschlichen Extremitätenskeletts, Morphol. Arb. **1**:517, 1891. (*b*) Gruber, quoted by Pfitzner.

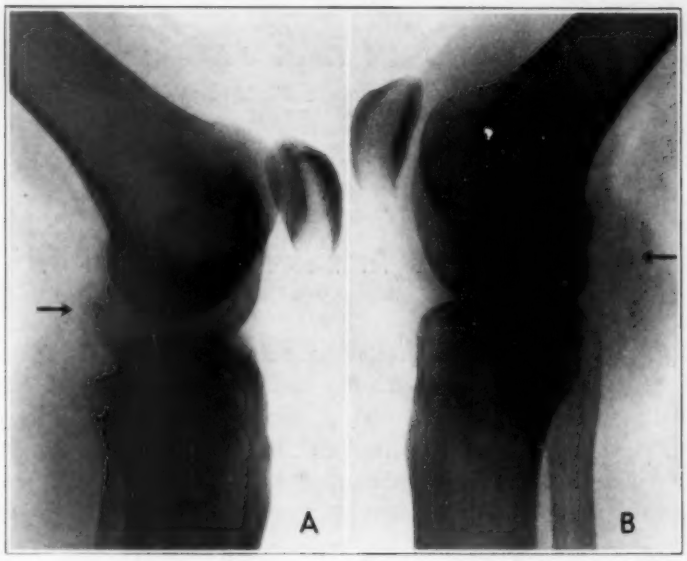

Fig. 1.—*A*, roentgenogram of the left knee. Note the normal position of the sesamoid. *B*, roentgenogram of the right knee (synovitis with effusion). Note the backward displacement of the fabella.

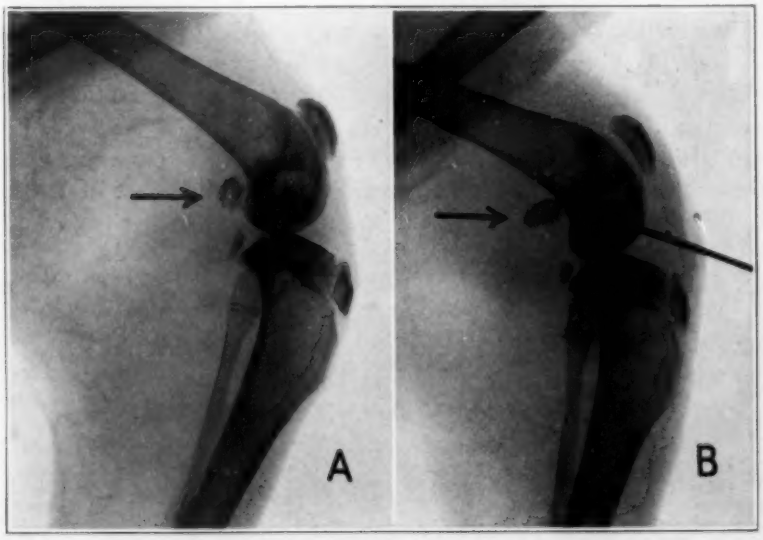

Fig. 2.—Roentgenograms of a rabbit's knee. In *A*, note the double femoral and the single tibial sesamoids. *B*, note the posterior and upward displacement of the femoral sesamoids after an intra-articular injection of saline solution.

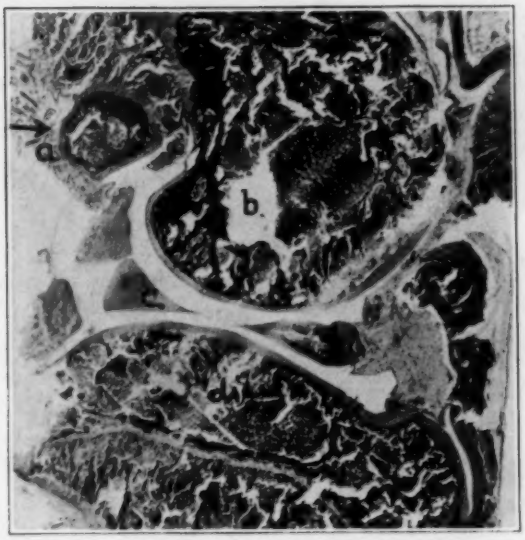

Fig. 3.—Photomicrograph of a vertical section through the knee joint of a young rat: (*a*) fabella; (*b*) femoral condyle; (*c*) semilunar cartilage containing normal bone; (*d*) tibia.

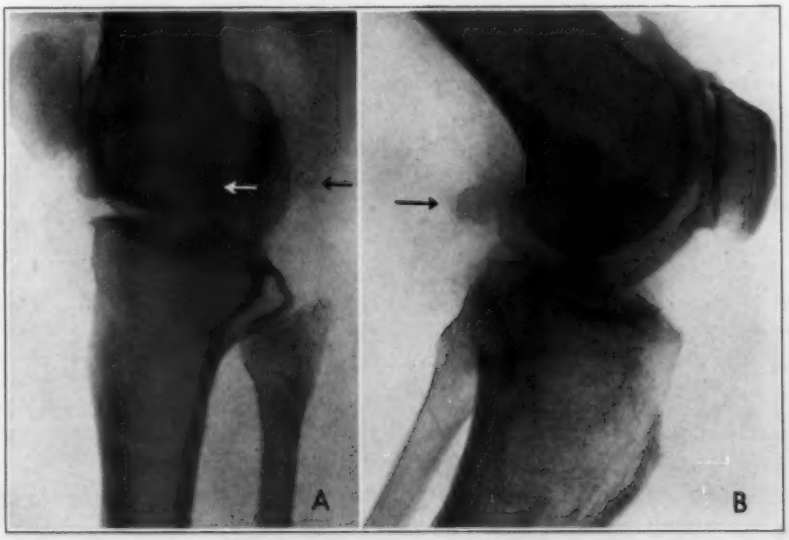

Fig. 4.—*A*, roentgenogram of the right knee. Note the presence of a medial and lateral sesamoid. *B*, roentgenogram of the right knee (osteo-arthritis). Note the irregular appearance of the fabella.

normal area of rarefaction in the external femoral condyle, the sesamoids are often seen by roentgen examination in the anteroposterior view. These ossicles vary in diameter from several millimeters to 2 cm. In roentgenographic pictures they appear usually semilunar in the lateral view and either elliptic or circular in the anteroposterior projection. Many variations in shape, however, exist.

ROENTGENOGRAPHIC OBSERVATIONS

In this study, 806 roentgenograms of the knee joints of 700 patients were examined. First, we wanted to determine the incidence of fabellae in this number of patients, each of whom had symptoms referable to one or both knee joints. Second, we desired to study variations in the appearance of the ossicles. Third, we sought to ascertain whether their

Summary of Data on Which Study Was Based

Age, Years	Patients Without Fabellae	Patients with at Least a Single Fabella	Patients Examined	Incidence (by Roentgenographic Examination) of at Least a Single Fabella, per Cent
1 to 10	71	0	71	0
11 to 20*	90	2	92	2
21 to 30	89	13	102	12
31 to 40	108	15	123	12
41 to 50	128	19	147	12.9
51 to 60	95	22	117	18.8
61 to 70†	30	9	39	23
71 to 80	7	1	8	12.5
81 to 90	1	0	1	0
Total	619	81	700	11.5

* A fabella was seen roentgenographically in a boy 12 years of age.

† The higher incidence of fabellae in the older groups can be attributed possibly to calcification or ossification of previously existing sesamoids that originally were not sufficiently calcified to be visualized roentgenographically.

presence was of any aid in the diagnosis of lesions in or about the knee joint.[2]

Only 106 patients had had roentgenograms taken of both the right and the left knee. Nineteen of these patients had fabellae. Sixteen had bilateral fabellae (one ossicle in the external head of the right and the other in that of the left gastrocnemius muscle). Two others had only one sesamoid (one patient having it in the lateral head of the right and the other in that of the left gastrocnemius muscle). One had sesamoids in the lateral and medial heads of the right gastrocnemius muscle (fig. 4 *A*). In these 106 patients the incidence of bilateral fabellae (a sesamoid in the external head of the right and one in that of the left gastrocnemius muscle) was about 15 per cent.

In 318 cases the right knee alone was roentgenographed (in the usual projections), and single sesamoids were present in 36 cases (about 11 per cent). The roentgenographic examination of the left

2. In these studies Dr. H. L. Jaffe gave helpful criticism.

knees of 276 additional patients showed an ossicle in the lateral head of the gastrocnemius muscle in 26 instances (about 9.5 per cent). Thus, in our group of 700 patients, 345 of whom were males and 355, females, the incidence by roentgenographic examination of at least a single fabella was 11.5 per cent for each sex.

The accompanying table gives the age grouping of the patients and the percental incidence in each group of at least a single fabella.

In 193 patients there was osteo-arthritis of the knee. Thirty-eight of these had at least a unilateral fabella (19 per cent). In 7 of these 38 patients, irregularities in the sesamoids suggesting arthritis were noted (fig. 4 *B*). Among 9 cases of synovitis of the knee of unknown origin in which fabellae were seen, there was abnormal displacement of the fabella in 4 cases (fig. 1 *B*). An irregular large fabella was noted in the roentgenogram of the knee of a patient suffering from gout. The ossicle appeared to be involved in the disease process, as were the bones comprising the knee joint. In 2 cases of Paget's disease, the lateral sesamoid appeared within normal limits.

COMMENT

In the literature the incidence of the fabella has been reported as varying from 10 to 20 per cent. The higher figures were based on anatomic studies and the lower ones on roentgenologic investigations.[3] Fabellae seem to take part in pathologic processes. Some seem to become arthritic; some become involved in general metabolic disorders, as gout; some can be fractured,[4] while others become involved in what is described as osteochondritis.[5] A rare lesion is the pinching of the fabella in the knee joint, which is possibly due to a herniation of the posterior capsule.[6]

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3. Pancoast, H. K.: Radiographic Statistics of the Sesamoid in the Tendon of the Gastrocnemius, Univ. Pennsylvania M. Bull. **22**:213, 1909. Skinner, E. H.: Loose Body Versus Sesamoid Bone in the Outer Head of the Gastrocnemius, New York State M. J. **90**:153, 1909. Fischer, H.: Beitrag zur Kenntnis der Skelettvarietäten, Fortschr. a. d. Geb. d. Röntgenstrahlen **19**:43 (July) 1912. Ulrichs, B.: Fabella, Zentralbl. f. Chir. **53**:1369 (May 29) 1926. Simon, H.: Fabella, ibid. **53**:650 (March 13) 1926. Sonntag, E.: Zur Frage der Fabella, ibid. **54**:660 (March 12) 1927. Vogel, K.: Ein Fall von doppelter Fabella, ibid. **54**:2566 (Oct.) 1927. Pick, H.: Zur Frage der Fabella, ibid. **54**:1743 (July 9) 1927. Grassmuck, J.: Ueber das Vorkommen der Fabella, ibid. **55**:1031 (April 28) 1928. Gregory, A.: Ossiculum sesamoideum verum musculi gastrocnemii externi (Gruber), ibid. **55**:2518 (Oct.) 1928. Yano, K.: Das Os sesamoideum musculi gastrocnemii lateralis bei den Japanern, Folia anat. japon. **6**:241 (May) 1928. Kremser, K.: Beobachtung einer Fabella im lateralen und medialen Gastroknemiuskopf, Röntgenpraxis **2**:134 (Feb.) 1930.

4. Sagel, J.: Fracture of Two Femoral Sesamoid Bones, Am. J. Surg. **18**:507 (Dec.) 1932.

5. Lepoutre, C.: Sésamoïde douloureux (sésamoïde du jumeau externe). Guérison par l'extirpation, Rev. d'orthop. **16**:234 (May) 1929.

6. Heydemann, H.: Die Fabella, Röntgenpraxis **1**:950 (Dec.) 1929.

Commonly we see the coexistence of fabellae with intra-articular bodies. The sesamoids are usually differentiated by their bilateral symmetry in size, shape and location. Reports have been cited in which it was stated that fabellae considered as intra-articular bodies were surgically removed.[7] An important method for the differentiation of intra-articular and extra-articular bodies is that of roentgenographic examination of the knee joint after sufficient amounts of opaque material, saline solution or air have been injected.[8] In figure 2 *B*, the fabellae of the rabbit are seen displaced backward and upward by the injected fluid. A similar condition is presented clinically in figure 1 *B*, in which the ossicle is seen displaced posteriorly by the effusion. In addition, displacement of the sesamoid should be an important sign in the detection and location of tumors or cysts of the soft tissues about the posterior portion of the knee joint. Thus, a swelling originating intra-articularly may, if large enough, displace the fabellae posteriorly. A mass in the gastrocnemius muscle or in the posterior capsule, however, may force the fabellae toward the knee joint. The sesamoid of the gastrocnemius muscle must, in addition, be differentiated from chip fractures, paracondylar and meniscal calcifications or ossifications, calcified glands and calcified blood vessels.

SUMMARY AND CONCLUSIONS

(*a*) A study of roentgenograms of the knee joints of 700 patients revealed the presence of at least a single fabella in 11.5 per cent.

(*b*) The sesamoids seem able to undergo pathologic alterations such as arthritis, fracture or osteochondritis.

(*c*) The fabella may be a bony landmark (as evidenced by roentgenographic examination) for the recognition of effusions into the knee joint and for the differentiation of swellings or masses near the posterior ligament of the knee joint.

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7. Wolff, H.: Ueber die praktisch chirurgische Bedeutung des Sesambeines im Musculus gastrocnemius, Berl. klin. Wchnschr. **41**:1052, 1904. Flecker, H.: Roentgenographic Observations of the Time of Appearance of Epiphyses and Their Fusion with the Diaphyses, J. Anat. **67**:118 (Oct.) 1932.

8. Oberholzer, J.: Die Arthro-Pneumoradiographie, Beitr. z. klin. Chir. **158**: 113, 1933.

EPILEPSY SECONDARY TO HEAD INJURY

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That trauma to the head may produce epileptic seizures is a well known fact, but to ascertain in a given case of generalized epilepsy whether the epilepsy may reasonably be considered due to a previous head injury or whether it is of a nontraumatic type is not always easy. The following report of a case exemplifies such a problem:

A Negro man, aged 36, an electrician's helper, reported for examination with the complaint of generalized convulsions. Fourteen months previous to entrance, the head of a hammer flew from the handle while he was driving a nail and struck him in the right parietal region of the skull. He suffered an abrasion of the scalp, but there was no deep laceration, and sutures were unnecessary. Roentgenograms did not reveal a fracture. The patient was dazed, but there was considerable doubt as to whether he was unconscious at the time of the injury; if he was unconscious, it was only momentarily. He returned to his duties the next morning and continued to work for a period of sixteen months. He was then discharged on account of economic conditions. On his discharge he applied for compensation, stating that convulsions had developed three months after the injury, which he believed were a result of the trauma. His story was doubted and a detective investigation carried out. The investigator was able to establish the occurrence of the first convulsion as being five weeks after the injury; he could not find any evidence of convulsions prior to the injury. Examination by us fourteen months after the injury revealed definite proof of generalized seizures which were preceded by an aura which consisted of a peculiar abdominal sensation extending upward to the head; this was preceded by a cry and followed by generalized tonic contractions; the contractions, in turn, were succeeded by clonic spasms. There was loss of sphincter control involving both the rectum and the bladder. The patient then remained unconscious for a period varying from one-half hour to several hours, and it was several days before he returned to normal. During the examination it was evident that this man was untruthful but exceedingly shrewd, evasive and unreliable. Physical and neurologic examinations, as well as laboratory tests, revealed no abnormalities.

The case was settled for the sum of $1,700.

At a reexamination by us thirty months after the injury the patient reported a marked increase in the severity and frequency of the convulsion, intense headaches and fatigue so marked that he was totally incapacitated. Examination indicated evasiveness to questions and definite attempts to mislead the examiner. Again neurologic and physical examinations revealed no abnormalities. A ruling of the Industrial Accident Commission did not permit a reopening of the case in view of the fact that a compromise settlement and release had been made.

Presented before the Neurological Section at the Sixty-Second Annual Session of the California Medical Association, Del Monte, April 27, 1933.

Four questions of importance confront one in the study of generalized traumatic epilepsy, the solution of which we shall consider in this paper, which is based on a review of our series of cases of head injury, as well as on a study of the literature:

1. Did the head injury cause the epilepsy?

2. Following a head injury, how far may one go in prognosticating the probability that epilepsy will or will not develop as a result of the injury?

3. Is there any method of preventing the occurrence of this sequela?

4. Is there any method of therapy to be advised for traumatic generalized epilepsy?

CLASSIFICATION OF EPILEPSY

Epilepsy secondary to trauma may be divided into four types: (1) focal epilepsy; (2) generalized epileptic states, including both grand mal and petit mal; (3) so-called "hystero-epilepsy," and (4) reflex epilepsy. The differentiation is not always absolute, and in a case in which the condition primarily belongs to one of these groups there may be occasional seizures similar to those of one of the other groups.

A question rarely arises with regard to the etiologic rôle of the preceding trauma in any of these types, except in cases in which the convulsions are generalized. Our study is therefore concerned chiefly with this form. We shall, however, in a cursory manner consider the other three types.

Focal.—Focal, or jacksonian, epilepsy is a type which involves purely or primarily a certain localized area of the body, perhaps spreading from this to include the entire organism. It has been established by the work of numerous investigators that head trauma may produce pathologic changes in the brain in cases in which there are no neurologic signs as well as in those which present abnormal objective findings.

When a patient has a convulsive seizure of this form, it is important to study the seizure carefully as to both objective and subjective elements. By so doing the seizure may be classified into a focal group, and therapeutic measures may be directed toward a definite part of the brain. Hughlings Jackson first described the motor type, and for this reason the motor attack has been termed jacksonian epilepsy. Foerster [1] has verified the type of seizure and its point of origin by electrical stimulation of the cortex in conscious patients. This work has also been carried out by Penfield.[2] With this concept in view, Penfield and

1. Foerster, O.: Die Pathogenese des epileptischen Krampfanfalles, Deutsche Ztschr. f. Nervenh. **94**:15, 1926.

2. Penfield, W.: The Mechanism of Cicatricial Contraction in the Brain, Brain **50**:499, 1927.

Gage [3] have placed under the headings of epileptic seizures, or fits, the following manifestations: (1) clonic and tonic spasm; (2) paresthesias of the limbs or of the body; (3) hallucinations of sight, sound, smell and taste; (4) certain disturbances of consciousness and dream states; (5) visceral sensations (epigastric and thoracic), and (6) autonomic phenomena (such as disturbances of respiration, heart beat, secretion of tears, perspiration and flushing).

Deviation of the head and eyes to the side opposite the hemisphere involved is a valuable lateralizing sign. Seizures due to involvement of the frontal lobe are characterized by a loss of consciousness, followed by a turning of the eyes, head and body to the opposite side and by a simultaneous convulsion of the opposite lower extremity. In cases of involvement of the precentral gyrus, consciousness is usually lost late, and a tingling sensation may follow the jacksonian attack. In general, turning without aura points to a localization in front of the precentral convolution and turning with aura points to an area behind it. Involvement of the precentral convolution results in local clonic spasms with late loss of consciousness. Seizures arising in the postcentral convolution consists of numbness, tingling or a loss of sensation. Seizures beginning in the occipital lobe often have as their first phenomenon an optical aura such as flame, stars, light, etc., generally in the opposite visual field. Involvement of the temporal lobe may produce buzzing sounds and dizziness, as well as dreamy states, and if the uncinate gyrus is involved, the occurrence of peculiar odors.

In one article Foerster and Penfield [4] described a series of twelve clinical cases in which they demonstrated remarkable verification, on surgical tests, of the theoretical areas of localization and confirmed the origin of attacks in this type of epilepsy.

An epileptic attack is fundamentally an active process of stimulation and not a release phenomenon. The cicatrix, after injury to the brain or meninges, is primarily a network of fibrous astrocytes which, as time passes, becomes vascularized, with replacement of nerve cells and fibers by connective tissue. The time of onset of the convulsions after injury in 12 cases was from five months to fourteen years, at which time the vascular plexus of the involved area is well developed while the nerve fibers are much diminished. It appears, accordingly, that the initiation of the seizures is associated with the vascular condition rather

3. Penfield, W., and Gage, L.: Cerebral Localization of Epileptic Manifestations, Arch. Neurol. & Psychiat. **30**:728 (Oct.) 1933.

4. Foerster, O., and Penfield, W.: Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle und für die therapeutische Bekämpfung derselben, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:475, 1930.

than with the nervous elements and that the scar must involve traction on the blood vessels. Foerster and Penfield suggested the hypothesis that a vasomotor reflex, secondary to this traction, is responsible for the initiation of convulsive seizures.

Penfield [2] and Foerster [5] have demonstrated as regards man, and Wortis,[6] as regards animals that after an injury to the brain, if the damaged tissue is not removed, a scar rapidly forms composed of connective tissue and fibrous astrocytes with a marked vascular plexus. The scar becomes adherent to the meninges on the one hand and to the brain on the other. As time advances, it constantly contracts, causing a pull on the cerebral tissue. As this process continues, enlargement of one or both ventricles with internal hydrocephalus often develops, and frequently both ventricles become displaced to the side of the lesion, thus causing the so-called "wandering ventricles."

Foerster and Penfield [7] have pointed out the value of encephalography and also have made the following surgical recommendations: In cases of traumatic epilepsy all the involved tissue of the dura mater and of the brain should be excised. The excision must be extensive enough to remove any scar tissue and all the altered tissue. If the ventricle has been enlarged or displaced toward the side of the lesion so as to have reached almost to the surface, it must be incised and widely opened. Foerster and Penfield have experimentally demonstrated that a smooth excision of brain tissue does not cause new scar tissue to form. They repair the dura mater by plastic surgery with the use of fascia lata and leave the orifice in the bone of the skull open. Glaser, Thienes and Beerman (an article is to be published later) have demonstrated experimentally on animals that animal membrane is just as efficient as fascia lata.

Focal epilepsy develops from numerous causes other than trauma to the brain. Abscesses, tumors and adhesions may cause this symptom complex.

Hystero-Epilepsy.—"Hystero-epilepsy," admittedly, is a poor term, but it is descriptive of one type of the disease and serves tentatively as a useful classification. We do not desire to enter into a discussion of the question as to the fundamental etiologic unity of the so-called hystero-epilepsy, affect epilepsy and alcohol epilepsy, which has

5. Foerster, O.: Encephalographische Erfahrungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **94**:515, 1924.

6. Wortis, S. B.: Head Injuries: Effects and Their Appraisal; Experimental Studies of Induced Convulsions and Ventricular Distortion in the Cat, Arch. Neurol & Psychiat. **27**:776 (April) 1932.

7. Foerster, O., and Penfield, Wilder: The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99, 1930.

been studied in detail by Notkin.[8] There are undoubtedly certain persons in whom convulsive attacks have developed after trauma who present one or more of the stigmas of hysteria or other evidence of functional nervous disorder; the attacks follow the types described by Osler [9] and other authors of textbooks as hysterical as opposed to truly epileptic, and the course and response to treatment are similar to other objective phenomena occurring in hysteria. We have included such forms under the term hystero-epilepsy.

Reflex.—Reflex epilepsy is epilepsy with periodic attacks due to peripheral injury. It may be preceded by an aura. Removal of the peripheral scar stops the attack (Siemerling [10]).

It is noteworthy in reviewing the literature on epilepsy that there is a comparative lack of reports of cases of this type of epilepsy in the recent as compared with the earlier literature. This is perhaps due to a more scientific and accurate study of the cases, with consequent discovery of evidences of a cerebropathologic condition which is considered to be the probable cause of the convulsions. The record of a case of this type of epilepsy in a patient whom we have recently seen is as follows:

W. M., aged 37, a lumberman, eleven months before we examined him suffered an injury when a boom struck his right arm and chest, throwing him to the ground and causing complete paralysis of the right radial and left external popliteal nerves. Roentgenograms revealed a fracture of the right eighth, ninth, tenth and eleventh ribs in the axillary line, fracture of the superior and inferior rami of the pelvis on both sides and a comminuted fracture of the right ilium. Immediately following the injury the patient was operated on, and an attempt was made to suture the radial nerve. This nerve was again explored in December 1932 and scar tissue was removed. In February 1933 the external popliteal nerve was explored and found embedded in scar tissue. Several weeks before the last operation, the patient began to have attacks of jerking movements of the left leg. The attacks increased somewhat and became rather severe three weeks following the operation. The attacks came on spontaneously, although they could be brought on by galvanic stimulation over the scar of the operative incision. During examination a few days previous to the present writing an attack was brought on by galvanic stimulation in this area, which developed in the following manner: A few minutes after the current was applied the patient felt a peculiar sensation in his epigastrium. Very soon each muscle of the left thigh began to ripple. In a few seconds clonic contractions of the muscle fibers in this area appeared. After a few seconds of further contractions, the thigh flexed on the abdomen and the knee on the thigh. This spasm was tonic, and for a few minutes it was impossible for the leg to be passively extended. The arms became rigid at the sides of the body, and the elbows became flexed at a right angle. The patient complained of intense pain in the leg.

8. Notkin, J.: "Affecte Epilepsy" and "Hysteroepilepsy, Study of Convulsive States in Psychopaths, J. Nerv. & Ment. Dis. **72**:135 (Aug.) 1930.

9. Osler, William: Principles and Practice of Medicine, ed. 11, revised by Thomas McCrae, New York, D. Appleton & Company, 1930.

10. Siemerling, quoted by Bowers, Paul: Traumatic Epilepsy, Internat. Clin. **4**:132, 1921.

He was conscious during the entire attack and answered questions. The face was flushed, and the muscles of the neck were under tension. Finally, with the aid of an assistant, the leg was straightened, and the attack subsided immediately.

Generalized Convulsions.—In order to obtain more definite criteria for assistance in arriving at a final decision as to whether a head injury is the causative factor in questionable cases for the onset of generalized convulsions, we have reviewed 300 articles in the literature, from which we were able to collect 65 satisfactory case reports, and 7 case records of our own. In analyzing the records of cases, we have eliminated those which we considered to be of nontraumatic epilepsy; those of definite jacksonian character, in most of which the condition was due to bony spicules, abscess, intracranial hemorrhage or some other localized pathologic condition, and those of hystero-epilepsy and reflex epilepsy. An effort has been made to determine: (1) the relationship between the severity of the injury and the onset of the convulsions and (2) the time of onset of the convulsions.

REPORT OF CASES

CASE 1.—*History.*—L. G., an American, aged 27, a mechanic, reported for examination on Nov. 18, 1929, with the complaint of attacks of unconsciousness, headache and vertigo.

The patient's history and the family history were essentially unimportant.

Seventeen months previously the patient was struck on the head or the back by a falling timber (the witnesses differed as to whether the head or the back was struck). He became unconscious at once and did not remember anything until two weeks later; he was in the hospital for one month and was then discharged to return to work. After the injury he had attacks of frontal headache and dizziness which occurred especially when he was stooping. He tired easily, and occasionally objects became blurred before his eyes. He slept poorly. Memory was good for past events, but he was forgetful in carrying out orders. He had difficulty in holding positions as a mechanic because he fell asleep and did not carry out accurately a simple mechanical procedure.

Six months before presenting himself for treatment he began to have attacks of unconsciousness; he had eight such attacks in all. A definite aura always preceded them. Occasionally he felt that he was going away in a dream and became unconscious; at other times something seemed to be pulling him forward in terrific jerks and he became unconscious at about the third jerk. On one occasion he chased a friend around the room and tore his shirt off. His last attack was at home, two weeks before presentation. He called his brother, and when the latter arrived he was unconscious and rigid; his eyes were closed, his face red and his breathing rapid. This lasted three minutes; he then said a few words and went to sleep. It generally required about twenty-four hours for him to become normal after an attack, but he was up and about in an hour. He was often confused after this hour.

Physical Examination.—The patient was a well developed, well nourished man. The pulse rate was 86; the temperature, 98.6 F.; the blood pressure, systolic 125 and 80 diastolic; the height, 5 feet and 5½ inches, and the weight, 149 pounds (67.6 Kg.). He had several moles. The hair, eyes and ears were normal. The tonsils were buried and the pharynx reddened. The teeth were in good condition. The neck, heart, lungs, abdomen, spine and extremities were all essentially normal.

Neurologic Examination.—Cranial Nerves: There were fine tremors of the eyeballs on lateral, upward and downward movements. The corneal reflex was present. The condition was suggestive of, but not true, nystagmus. The pharyngeal reflex was diminished and the palatal reflex absent; otherwise the cranial nerves were normal.

Frontal Lobes of the Brain: The patient was apparently not exceedingly bright, but he appeared to be sincere. He was not of a quarrelsome nature, but when insulted would fight. However, he had had only a few fights. The other lobes of the brain were essentially normal. The patient had a strong grip, equal in the two hands.

Reflexes: The abdominal, patellar and achilles tendon reflexes were slightly exaggerated and equal on the two sides; otherwise all the reflexes were normal. There were no pathologic reflexes.

Roentgen Examination.—Roentgenograms revealed a fracture of the right occipital bone and also one of the right fourth and fifth metacarpal bones, with some union of the latter. Roentgenograms of the spine revealed no abnormalities.

Diagnosis.—The original injury was diagnosed as fracture of the skull, cerebral concussion and fracture of the right fourth and fifth metacarpal bones.

The later condition was diagnosed as posttraumatic cerebral syndrome, posttraumatic neurosis, possible posttraumatic epilepsy, with partial disability for work. Treatment with phenobarbital was instituted.

Course.—On December 6 there had been no attack of unconsciousness during the preceding three weeks. The memory was still poor; the dizziness and staggering gait had slightly increased, and the patient was drowsy during the day. We felt that the phenobarbital had probably stopped the attacks but had made him drowsy and increased the dizziness. The dose was decreased to ¼ grain (0.016 Gm.) four times a day.

On December 19 the diagnosis of epilepsy was considered, to be confirmed. There had been no attacks since the first examination on Nov. 18, 1929, probably owing to the constant use of phenobarbital. The only complaint was occasional attacks of dizziness when the patient was quiet. The diagnosis was posttraumatic epilepsy and posttraumatic cerebral syndrome.

On Feb. 3, 1930, it was discovered that the patient had had two attacks of epilepsy since the last examination; one eleven days before and the other four days before, when he forgot to take his medicine. Physical examination and neurologic examinations gave the same results as at the first examination on Nov. 18, 1929. The patient was given phenobarbital, ¼ grain (0.016 Gm.) three times a day and ½ grain (0.033 Gm.) once a day.

He was seen periodically until July 11, 1932. He was kept on phenobarbital, which was given in quantities small enough to avoid drowsiness, until Feb. 4, 1931, when the drug was discontinued and he was given a placebo. Since August 1930 he has apparently been able to do any kind of work on the ground. He had two convulsive seizures in June and July 1931, the first ones since February 1930, but he had none after that. He is now free from complaints. Recent physical examination and neurologic examinations revealed no abnormalities. He has received no sedative medication since February 1931. He was discharged on that date as well, without permanent disability.

Case 2.—V., an American man, aged 42, an oil-worker, was struck on the right side of the face by a pair of tongs weighing 125 pounds (57 kg.). The right maxilla was fractured; there was no fracture of the cranium. The patient was unconscious for three minutes and dazed for three hours. Three weeks after the

injury he began to have attacks of petit mal, which would consist of momentary mental confusion, with loss of memory and inability to think or to comprehend what he was reading. These attacks have occurred from two to four times a day ever since they began. Eighteen months after his injury, the first grand mal attack developed. In the next twenty months the patient had about fourteen such attacks. The attacks are preceded by an aura, which does not occur with the petit mal attacks and which consists of a queer feeling, as of a "whirling around" in his head. If he is standing, he falls heavily and foams at the mouth. He becomes totally unconscious, has convulsive movements for two or three minutes and then passes into a stupor of varying duration. There is no history of an initial cry, of incontinence of urine or feces or of jacksonian attacks.

Physical examination revealed no abnormalities. The blood pressure was 102 systolic and 78 diastolic. The clinical and serologic tests gave negative results for syphilis; there were no signs of a tumor of the brain.

Twenty months after the injury, the patient was placed on a ketogenic diet and given medication with phenobarbital. For about six months he was free from grand mal attacks; then he became careless with his treatment and had one attack of grand mal. He was then free from attacks for eight months, during the last five months of which he did not follow the ketogenic diet but continued to take phenobarbital, bromide or other sedatives. This brings the case up to the present. A psychiatrist reported that the patient is retarded mentally. He has pursued no gainful occupation since his injury and is considered totally and permanently disabled.

Case 3.—K. H., a Japanese boy, aged 12 years, was run over by a truck when he was 3 years old, the wheels going over his head. He was apparently normal until he was 6 years old, when he had an attack of scarlet fever, after which he soon began to have mild spells of unconsciousness. These were often accompanied by vomiting, cold perspiration and a cold, clammy appearance. They occurred about twice a year, each lasting from a few hours to a day, and have not changed appreciably in character or severity since they first appeared.

Twenty-four days ago, the patient had an attack at school and was unconscious for fifteen minutes. He did not bite his tongue or become incontinent or froth at the mouth. Soon afterward a severe headache developed which lasted all day. Six days ago the patient had another attack, in which he did not lose consciousness but became very dizzy.

Physical examination showed no abnormalities except chronic follicular tonsillitis, marked postnasal discharge, chronic pain and sinusitis, especially of the maxillary antrums.

Neurologic examination revealed that the pupils were moderately dilated and that there was nystagmus on looking laterally to the right and the left. The patient was oriented as to persons, place and time; cooperation and attention were good. There was no weakness or paralysis. The abdominal, cremasteric, patellar and achilles tendon reflexes were all exaggerated and equal on the two sides. The Wassermann test of the blood was negative; the blood count was normal.

An encephalogram showed that the right ventricle was moderately dilated and the left ventricle contracted. There was a deformity of the anterior horn of the left ventricle. A greater amount of air than is present normally appeared over the occipital area, which suggested cortical atrophy. A later examination will be necessary to determine if a tumor of the brain is developing.

An otologist carried out the vestibular tests and reported that the results were suggestive of a lesion involving the intracranial vestibular pathways. He advised that the vertical nystagmus upward, which appeared occasionally when the patient

gazed at an extreme angle upward, be watched. He had no suggestion to make as to the nature of the lesion; he thought that it might have been produced by a toxemia, such as the scarlet fever from which the patient had suffered. He recommended tonsillectomy and treatment of the sinusitis.

Only one observation has been made of this patient to date. A diagnosis of convulsive seizures secondary to unilateral hydrocephalus and cortical atrophy was made, and it was advised that the patient be given phenobarbital and a limited amount of fluids.

CASE 4.—G. S., a man aged 68, married, a painter, fell 8 feet (2.4 meters), sustaining a fracture of the left parietal bone, with extradural hemorrhage, and also a fracture of one scapula and of a great toe. Roentgenograms showed a comminuted fracture of the vault; no operation was done. The patient was in the hospital for several months; he was unconscious for three days following the injury. Blood flowed from the left ear at the time of injury.

Two months after the injury the patient was improving mentally, and the wound was draining; he had difficulty in speaking at times. Three months after the injury, in attempting to turn over quickly, he became dizzy. He still had some difficulty in speaking; his hearing in the left ear was impaired, and he was dizzy and nervous. Four months after the injury some teeth were pulled, and the jaw was curetted. Seven months after the injury he was improving; during the following month he was still dizzy. Eight and one-half months after the injury, while at work, he suddenly fell, becoming unconscious. Following this he had the first headache since his injury. Nine and a half months after the injury arteriosclerosis and nephritis were diagnosed, and some of the attending surgeons stated the belief that these conditions may have accounted for some symptoms. A week later, a shooting pain developed over the left side of the head, with dizziness, and he again fainted. Eleven months after the injury, while driving a truck, he became unconscious and drove into a telegraph pole. Two weeks later, he complained of tinnitus and of dizziness of moderate severity when lying on his right side. He also suffered loss of memory and was irritable. The biceps reflex was slightly more active on the right, as were the triceps and radial reflexes. There was no Babinski sign.

Fourteen months after the injury, while he was eating in a cafeteria, his head and eyes were drawn to the right side and he became unconscious and fell to the floor, biting his tongue.

Three months later he was given phenobarbital because of another epileptic fit.

The case was terminated nineteen months after the injury by a permanent disability rating by the Industrial Accident Commission of 78.5 per cent disability, based on dizziness, limited motion of the shoulders, loss of hearing and retinal hemorrhage. He received $20.83 a week for forty weeks and a pension for the remainder of his life of $5.93 a week.

CASE 5.—A. J. S., a man aged 51, sustained a depressed fracture of the left frontal bone and a stellate fracture of the base of the skull just posterior to the left mastoid process. The patient was unconscious for six days following the accident; four days after the accident a subtemporal decompression was done. Complete anosmia developed immediately after the injury and persisted permanently. For four months after the injury there were some mental confusion and moderate euphoria, and the patient was easily excited. These mental developments were superimposed on an original low grade mentality and some neurasthenia. Impairment of hearing was noted about a year after the accident, and it gradually increased over a period of twelve months following its first appearance, being more

marked on the left side. One year after the injury the patient showed slow cerebration and some defect in memory for events long past, and these persisted. Atrophy of the optic nerve on the left side was definitely diagnosed eight months after the accident. Twenty-five months after the accident there appeared for the first time epileptiform attacks with cramping of the arms, legs and stomach. The patient complained of headaches, vertigo and blurred vision in the left eye continuously after the accident.

On examination there was a slightly exaggerated patellar reflex on the left side; a slight increase in the left biceps and achilles reflexes lasted for a year following the injury.

The patient received a permanent disability rating from the Industrial Accident Commission of 100 per cent about thirty-five months after the accident, for industrial blindness of the left eye, anosmia, impaired hearing of both ears, mental deficiency and traumatic epilepsy.

CASE 6.—R. W. H., a man aged 40, an iron-worker, fell 15 feet (6 meters) sustaining a transverse fracture of the occipital bone. The patient was unconscious; he remained in the hospital for eighteen days. Forty-nine months after the accident, fainting attacks developed; he would perspire over his entire body, his face would become pale and he would feel weak and fall on his knees. His entire head seemed to throb before an attack.

Neurologic examination revealed no abnormalities at that time. He had attacks of headache. During the second attack, the patient had a peculiar taste in his mouth, and vision became blurred. During the third attack he also had a peculiar taste. The attacks were of only momentary duration, and he felt entirely well afterward.

Tests of the spinal fluid one month after the attacks began gave negative results.

The patient was given phenobarbital. Fourteen months after the attacks began, they ceased, but if the dose of phenobarbital was decreased the patient had an olfactory aura. He was observed for thirty-two months after the onset of attacks, and in the last eighteen months of that period he had experienced no attacks, but had been given phenobarbital, generally 2 grains (0.13 Gm.) a day. Toward the end of that period he returned to work as an iron-worker.

This case was considered to be one of posttraumatic epilepsy with aura, the attacks being of the petit mal variety, which developed long after the injury.

CASE 7.—F. S., a man aged 45, was admitted to the hospital on March 3, 1933, and discharged on the same day.

The patient had received an injury to the head twenty-five years previously. Since then he had had epileptic attacks frequently. During an attack everything turned dark before his eyes and he fell to the floor, frothing at the mouth and biting his tongue. He complained of headache after regaining consciousness. The attacks began from two to three years after the injury.

The physical condition of the patient was normal. The blood pressure was 110 systolic and 70 diastolic. An encephalogram was to be made, but for reasons unknown it was not done.

The spinal fluid was clear, with 4 cells; there was a slight increase in the globulin, and the Wassermann test was negative.

The diagnosis was posttraumatic epilepsy.

COMMENT

The study of the articles reviewed was begun with the purpose of obtaining data based on complete histories of cases, but this has been

extremely disappointing; the records of cases have been incomplete, details necessary for careful analysis being absent. In many instances no attempt has been made to differentiate focal epilepsy from generalized epilepsy. The majority of the articles are statistical summaries containing occasional records of cases. The conclusions drawn from single reports of cases in some instances have been biased and opinionated and not based on the facts presented by the case. However, aside from these difficulties, several excellent detailed reports comprising analytic studies of large numbers of cases of epilepsy, chiefly from bullet wounds received in war, have appeared in the literature of the last decade.

As may be noted from the following statistics, epilepsy occurs with sufficient frequency following injury to the head to be of

Statistics on Epilepsy

Author	Cases of Head Injury	Incidence of Epilepsy, Percentage	% General	Focal
Rawling	452	25	14	6
Steinthal and Nagel	639	28.9	—	—
Coleman	50	31	—	—
Villande	450	70	—	—
Vogeler	1,334	16.5	—	—
Levinger	229	13.1	—	—
Frazier and Ingham	200	12.5	—	—
Laffier and Gullian	4,262	10.14	—	—
Villaret and Bailby	500	7	—	—
Reichman	600	3.8	—	—
Addie and Vagstaffe	610	6	—	—
Neuhof	175	1.7	—	—
Bowers	3,000	3.3	—	—
Wilson	18,000	5	—	—
Glaser and Shafer	325	5.8	1.8	1.5
Redlich (review of the literature)	...	20	—	—
Cobb (review of the literature)	...	4	—	—

clinical importance. On the other hand, there is a great variance in statistics as to the number of patients in whom posttraumatic convulsions develop.

In Rawling's [11] series of 452 cases of wounds of the head, epilepsy occurred in 25 per cent. The attacks in 57 per cent of the cases were generalized; in 25 per cent they were jacksonian.

Steinthal and Nagel [12] reported 639 cases of bullet wounds of the brain from injuries received in war, in 28.9 per cent of which typical epilepsy developed. In another 6.6 per cent of the cases the patient showed some epileptiform symptoms. Steinthal and Nagel divided their cases into primary cases, in which the epilepsy occurred at once or nearly so; i. e., either at the time of the injury or during the healing of the

11. Rawling, L. B.: The Remote Effects of Gunshot Wounds of the Head, Brit. J. Surg. **10**:93, 1922.

12. Steinthal, E., and Nagel, H.: Die Leistungsfähigkeit im bürgerlichen Beruf nach Hirnschüssen mit besonderer Berücksichtigung der traumatischen Epilepsie, Beitr. z. klin. Chir. **137**:361, 1926; **143**:35, 1928.

wound, and into secondary cases, in which the epilepsy occurred after healing. They found that 62.7 per cent of the cases of epilepsy belonged to the primary division and 37.3 per cent to the secondary. In 6.4 per cent of the epileptic patients the disease did not develop until four years or more after the injury.

Coleman [13] reported an incidence of epilepsy of 31 per cent in 50 cases of head injury.

Villande [14] reported epileptic seizures in 70 per cent of 450 cases of cranial wounds.

Vogeler,[15] in 1,334 cases of bullet wounds of the skull, found that epilepsy occurred in 16.5 per cent.

Redlich, quoted by Vogeler, in a review of the entire literature described traumatic epilepsy as occurring in from 15 to 20 per cent of the cases of wounds of the head.

Levinger,[16] of 229 cases of head injury, found that epilepsy developed in 13 per cent, while Frazier and Ingham [14] reported that of 200 cases of gunshot wounds of the head epilepsy developed in 12.5 per cent.

Tuffier and Gullian, quoted by Frazier and Ingham,[17] at the Third Interallied Congress held in Val-de-Grace, on Nov. 5, 1917, reported that epilepsy occurred in 10.14 per cent of 4,262 cases.

Cobb [18] stated that traumatic epilepsy occurred in about 4 per cent of cases of injury to the head.

Villaret and Bailby [19] found epilepsy in 7 per cent of 500 cases; Collier,[20] in from 5 to 8 per cent of his cases, and Reichmann,[21] in 3.8 per cent of 600 cases. Wagstaffe and Adie,[22] in a publication of the

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13. Coleman, C. C.: The Late Results of a Series of Head Injuries, Virginia M. Monthly **48**:235 (Aug.) 1921.

14. Villande, C.: Healing of Skull Wounds, Arch. de méd. et pharm. mil. **68**: 546 (Oct.) 1917.

15. Vogeler, K.: Das Spätschicksal der Schädelschussverletzten, Deutsche Ztschr. f. Chir. **234**:245, 1931.

16. Levinger, Louis: Untersuchungen an 30 durch Unfall Hirnverletzten mit epileptiformen Erscheinungen, Arch. f. orthop. u. Unfall-Chir. **31**:372, 1932.

17. Frazier, C. H., and Ingham, S. D.: A Review of the Effects of Gunshot Wounds of the Head, Arch. Neurol. & Psychiat. **3**:17 (Jan.) 1920.

18. Cobb, Stanley: Causes of Epilepsy, Arch. Neurol. & Psychiat. **27**:1245 (May) 1932.

19. Villaret, M., and Bailby, J.: Results in Five Hundred Cases of Cranial Cerebral Trauma, Ten to Twelve Years After Injury, Presse méd. **35**:289 (March 5) 1927.

20. Collier, James: Discussion of the Nature and Treatment of Epilepsy, Brit. M. J. **2**:1045 (Dec. 6) 1924.

21. Reichmann, V.: Occurrence and Frequency of Epileptic Seizures After Skull Fractures, Deutsche Ztschr. f. Nervenh. **96**:260, 1927.

22. Wagstaff, W. W., and Adie, W. J.: Notes on a Series of One Hundred and Sixty-One Cases of Gunshot Wounds of the Head Treated at No. 7, General Hospital, May to Aug. 1916, J. Roy. Army M. Corps **31**:307, 1918.

Medical Research Committee of Great Britain, reported epilepsy in 6 per cent of 610 cases.

Neuhof [23] had "statements of epilepsy" in 3, or 1.7 per cent, of 175 cases.

Bowers,[10] in a review of 3,000 cases of head injury, found that the incidence of epilepsy was 3.3 per cent.

Wilson [24] found epilepsy in 5 per cent of 18,000 cases.

Glaser and Shafer,[25] on investigation of 325 cases, found traumatic epilepsy in 19, or 5.8 per cent; in 6, or 1.8 per cent of the total number, the attacks were generalized; in 5, or 1.5 per cent, they were focal, and in 8, or 2.4 per cent, the condition was diagnosed as hystero-epilepsy. We have described our seven cases of generalized traumatic epilepsy in detail earlier.

It has been determined by this analysis that generalized convulsions may occur within the first ten days after injury. The important factor in regard to these early convulsions is that in every case the injury was of great severity. Kaldewey,[26] from his investigation, decided that these cases are extremely rare. Vogeler,[18] in a review of 743 cases of gunshot wounds with 163 cases of epilepsy, found 18 in which early convulsions developed. Every patient had received unusually severe head injury which was associated with fracture of either the base or the vault.

Foerster, in 1926, stated that immediate epileptic attacks could follow trauma of the head but would occur only in cases of severe injuries, such as fracture, hematoma or foreign bodies within the brain.

One may conclude from our statistical study, as well as from the opinion of the various authorities, that early convulsions must be associated with severe injury to the brain. For this reason any case in which epileptic seizures of the generalized type develop after a minor injury, as in the case which we have reported, within a period of several weeks would immediately be excluded from the posttraumatic group.

Further investigation of these cases brought out only one outstanding feature: In all the cases in which generalized epilepsy developed, the injury was of great severity.

Muskens [27] stated the belief that the diagnosis of traumatic epilepsy must be reserved for cases in which a fracture of the skull exists.

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23. Neuhof, Harold: Treatment of Craniocerebral Wounds and Its Results, Ann. Surg. **72**:556 (Nov.) 1920.

24. Wilson, S. A. K.: The Rôle of Trauma in the Etiology of Organic and Functional Nervous Disease, J. A. M. A. **81**:2172 (Dec. 29) 1923.

25. Glaser, M. A., and Shafer, F. P.: Skull and Brain Trauma; Their Sequelae, J. A. M. A. **98**:271 (Jan. 23) 1932.

26. Kaldewey, W.: Zur Frage der Frühepilepsie nach Unfall, Monatschr. f. Unfallh. **37**:161 (April) 1930.

27. Muskens, L. J. J.: Epilepsy, New York, William Wood & Company, 1928.

Fracture of the skull or unconsciousness for a relatively long period existed in all the cases. None of the patients had merely a slight laceration of the scalp. In very few of the cases did generalized epilepsy develop within the first five or six months, except in those cases in which it developed within the first ten days. The generalized epileptic seizures developed six months or more after the injury. In the article by Vogeler it was reported that the convulsive seizures developed primarily in a period of from six months to two years after the injury, but additional cases developed at an average rate of 0.22 per cent, or 1 in 445, until the seventeenth year after the injury. This was also found by us.

Throughout the literature there are numerous reports of cases of epilepsy developing at this late period. Of course it is difficult to ascertain the relationship between an alleged head injury and epilepsy which has developed about seventeen years afterward. From the war statistics it appears that this is possible.

It is the belief of some authors, though without substantiation, that the production of epilepsy is dependent on a special tendency for spasms to develop in a particular person and that the injury acts merely as an exciting or culminating factor.

It is apparent from our studies that posttraumatic generalized epilepsy may occur within the first ten days or so following a head injury in which the trauma is markedly severe and that in a period of from five to six months thereafter it does not often occur. Any case in which generalized epilepsy develops during that period should not be classified as of traumatic origin until such an origin is definitely proved. This fact is of interest from a pathologic standpoint and fits in with the development of changes in the brain (Naffziger and Glaser [28]).

The majority of the convulsive seizures develop within the first two years after injury. Posttraumatic epilepsy is rare. It occurs in approximately from 1.5 to 4 per cent of the cases. That it appears only in cases of severe trauma is to be expected, for, should it be prevalent in cases of minor head injuries, it would develop in practically every child.

PATHOLOGY

Injuries of the head may bring about various pathologic changes within the brain. It is impossible to state that many of them may be related to succeeding epilepsy. Which of these pathologic changes are responsible for late epilepsy one cannot state with any certainty. The literature has not revealed uniform pathologic changes which could account for the development of generalized epilepsy. For this reason,

28. Naffziger, H. C., and Glaser, M. A.: An Experimental Study of the Effects of Depressed Fractures of the Skull, Surg., Gynec. & Obst. **51**:17 (July) 1930.

we have briefly considered the various organic changes which are known to exist in the brain following trauma. It is possible that any of these may be responsible for generalized epilepsy, yet, on the other hand, it may again be true that such epilepsy, secondary to trauma of the head, may occur in a perfectly normal brain. These points to date have not been verified by a sufficiently extensive statistical study to justify any conclusions.

Much of our knowledge of the pathology of concussion is deduced from the more serious cases of head injury. There is the work of Trotter,[29] Head,[30] Cushing,[31] Mott,[32] Meyer,[33] Cassasa,[34] Adami [35] and Foix.[36]

There are numerous theories as to the mechanism by which these pathologic changes may be brought about. This is not within the scope of this paper.

Trotter and Head have described opacity of the arachnoid with slight distention from the fluid beneath. The brain is orange-colored as a result of extravasation of blood. This is found in cases of old unresolved contusions. In the more severe cases of brain injury, as described by Cushing, there is actual disorganization of the substance of the brain, with severe intracerebral hemorrhage.

Adolph Meyer described small foci of softening, or defects of the cortex, in the tips of the frontal or temporal lobes.

Cassasa described 5 cases which seemed to be true cases of concussion. At autopsy gross section showed many minute hemorrhages scattered throughout the brain, including the cerebellum. Microscopic examination showed areas of hemorrhage limited to the perivascular lymph spaces and others also within the immediate adjoining substance of the brain.

Osnato and Giliberti [37] remarked that the appearance of microscopic sections showed a striking similarity to the perivascular extravasation observed in epidemic encephalitis.

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29. Trotter, Wilfred: Shell Wounds of the Head, Brain **42**:353, 1919.

30. Head, Henry: Shell Wounds of the Head, Brain **42**:349, 1919.

31. Cushing, Harvey: A Study of a Series of Wounds Involving the Brain and Its Enveloping Membranes, Brit. J. Surg. **5**:565, 1918.

32. Mott, F. W.: War Neuroses and Shell Shock, New York, Oxford University Press, 1919, pp. 4, 5 and 38.

33. Meyer, Adolf: The Anatomical Facts and Clinical Varieties of Traumatic Insanity, Am. J. Insanity **6**:374, 377, 382 and 388 (Jan.) 1904.

34. Cassasa, C. B.: Multiple Traumatic Cerebral Hemorrhages, Proc. New York Path. Soc. **24**:101 (Jan.-May) 1924.

35. Adami, J. G., and Nicholls, A. G.: Principles of Pathology ed. 2, London, H. Frowde, vol. 2, p. 575.

36. Foix, Charles: Traumatic Lesions of the Skull and Brain, in Nelson Loose-leaf Medicine, New York, Thomas Nelson & Sons, 1920, vol. 6, p. 145.

37. Osnato, Michael, and Giliberti, V.: Postconcussion Neurosis; Traumatic Encephalitis, Arch. Neurol. & Psychiat. **18**:181 (Aug.) 1927.

Tanzi,[38] in cases in which the condition was classified as dementia traumatica, described small old hemorrhagic foci, transformed into cysts or into glial scars, diffuse chronic lesions of the nervous elements and chronic diffuse lesions of the vessels. He expressed the belief that following trauma lesions occur which later develop into the chronic processes of gliosis and degeneration.

With these changes, as described by Cassasa, it cannot but follow that certain mental and somatic symptoms will occur, developing with the secondary diffuse degeneration of glial and ganglion cells. The degree of this secondary diffuse process should determine the clinical phenomena that is interpreted as the posttraumatic cerebral syndrome. From experimental evidence, presumably the brain is sensitized so that sooner or later environmental influences produce additional symptoms which may be classified as psychoneurotic and are superimposed on the symptoms of the posttraumatic cerebral syndrome. This may result in hystero-epilepsy.

Naffziger and Glaser,[28] in experimentally produced cases of depressed fracture of the skull in rabbits, in which the animals were followed for a period of a year or more, demonstrated early cortical vascular changes due to the acute effects of the trauma. The acute pathologic condition cleared up within six weeks. At the end of eight months, deep-seated glial changes were noted directly beneath the site of injury, over the corpus callosum. The experiments were controlled by another set of animals in which depressions of the brain were produced by beads rather than by depressed fractures. In these no evidence of glial proliferation occurred. It is interesting to note that the clinical development of epilepsy occurs late and that the glial changes in the animals occurred late. What significance the deep-seated glial changes have in relation to the production of posttraumatic epilepsy has yet to be demonstrated, but the time limit is suggestive. There is a possibility that in posttraumatic epilepsy deep glial changes do occur over the corpus callosum, as in the animals.

Fay and Winkelman,[39] as the result of the observations of Bagley [40] that blood introduced into the subarachnoid space caused adhesions, expressed the belief that the pacchionian bodies were injured, with a resulting obstruction to the absorption of spinal fluid which caused secondary pressure atrophy of the cortex.

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38. Tanzi, Eugenio: A Text-Book of Mental Diseases, translated from the Italian by W. Ford Robertson and T. C. Mackenzie, New York, Rebman Co., 1909.

39. Fay, Temple, and Winkelman, N. W.: Pacchionian System; Histologic and Pathologic Changes with Particular Reference to Idiopathic and Convulsive States, Arch. Neurol. & Psychiat. **23**:44 (Jan.) 1930.

40. Bagley, Charles: Functional and Organic Alterations Following the Introduction of Blood into the Cerebrospinal Fluid, A. Research Nerv. & Ment. Dis., Proc. **8**:217, 1927.

Spielmeyer [41] has found in cases of epilepsy, whether essential or traumatic, changes within the cornu ammonis and the cerebellum. The changes were in the form of sclerosis. The sclerosis had the appearance of a thick, glial proliferation. In addition, there was loss of ganglion cells in definite areas. These were the late changes. Spielmeyer stated the belief that the relatively unsatisfactory blood supply to these parts causes them to suffer first, whereas in other parts of the brain, because of compensatory circulation, less reaction to the disturbance occurs. As all organic sources of these disturbances have been excluded, one must conclude that the vasomotor changes are influential in the mechanism of the epileptic attacks. As there is no evidence of stasis, the source must be vasospasm. This compares with the observations of Horsley, Dandy, Kennedy, Horrax and others, who have described sudden anemia and a decrease in the size of the brain at the beginning of each attack during exploratory craniotomy. These observations do not state the essential cause of the attack, but they help us to draw some conclusions about the mechanism.

Directly due to trauma there may be focal lesions with actual destruction of the brain, as has been described earlier in this paper. In addition, the immediate effect of generalized edema of the brain should be recognized. Rand and Courville [42] in fatal cases of injury of the head found increased vacuolation of the choroid epithelium and of the ependymal cells, with a variable degree of edema and with heightening of the individual cells. Occasional hemorrhagic extravasation was observed, but more frequently there was pigment in the stroma and epithelial vacuoles.

All these pathologic changes are secondary to hemorrhage, and the late effects are dependent on degenerative adhesions or glial proliferation secondary to the original hemorrhage. Were one to consider these pathologic changes the cause of the convulsions, there would be many more cases of epilepsy than exist. As one knows in proportion to the tremendous number of head injuries that occur epilepsy is in the minority and occurs following only the more severe type of injury.

The fact that a head injury sensitizes the brain so that extraneous circumstances may more readily bring on convulsions was shown by the work of Sauerback in 1913, who found that after trauma to the motor cortex smaller doses of cocaine produced convulsions than would produce convulsions in normal control animals. Dandy and Elman [43]

41. Spielmeyer, W.: Anatomic Substratum of the Convulsive States, Arch. Neurol. & Psychiat. **23**:169 (May) 1930.

42. Rand, C. W., and Courville, C. B.: Histologic Studies of the Brain in Cases of Fatal Injury to the Head, Arch. Surg. **23**:357 (Sept.) 1931.

43. Dandy, W. E., and Elman, Robert: Studies in Experimental Epilepsy, Bull. Johns Hopkins Hosp. **36**:40 (Jan.) 1925.

showed the same phenomenon, using absinth as a convulsant. Pike,[44] Muskens,[27] Wortis and McCulloch [45] and Wortis [6] confirmed this.

Jones and Langdon,[46] in the vestibular studies of epileptic patients, have found vestibular impairment and abnormalities. In practically all of these cases the vestibular deficiency was central; there was a subnormal constitutional response in 20 of 28 cases after turning, and after douching the constitutional responses were subnormal in 21 of 28 cases.

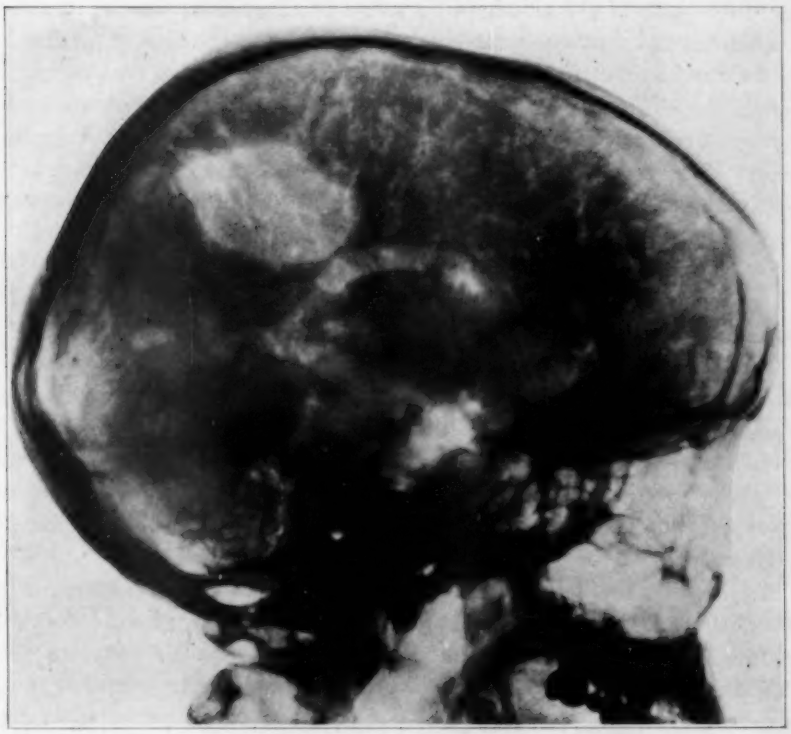

Fig. 1.—Roentgenogram showing posttraumatic epilepsy secondary to a depressed fracture of the skull. There are contraction of the ventricles and also cortical atrophy.

Rand and Linthicum,[47] while making a study of 35 cases found definite evidence of vestibular abnormalities. Glaser in a study of 65 cases

44. Pike, F. H., and others: Some Observations on Experimentally Produced Convulsions, Am. J. Psychiat. **10**:67 (Jan.) 1931.

45. Wortis, S. B., and McCulloch, W. S.: Head Injuries; An Experimental Study, Arch. Surg. **25**:529 (Sept.) 1932.

46. Langdon, H. M., and Jones, I. H.: Intimate Relations Between the Ear and Eyes, as Shown by the Bárány Tests, Arch. Ophth. **47**:348 and 354 (July) 1918.

47. Rand, C. W., and Linthicum, F.: Neuro-Otological Observations in Concussion of the Brain, Arch. Otolaryng. **13**:785 (June) 1931.

also found vestibular changes in 75 per cent of the patients. Of course no conclusions can be drawn from these findings other than that abnormalities existed which would indicate some disturbance in the central vestibular pathways.

Encephalographic changes in the form of distortion of the ventricles, unequal ventricles, atrophy or arachnitis have been found (figs. 1 to 4).

Fig. 2.—Roentgenogram showing posttraumatic epilepsy with a ventricular shift secondary to cerebral trauma and cortical atrophy.

It is true that in many of these cases there was a normal encephalographic picture. Grant,[48] in a review of 123 cases of epilepsy, of which 51 were posttraumatic, found that in 9.8 per cent of the traumatic group the encephalograms were normal. Atrophy and arachnitis were equally divided, while ventricular asymmetry occurred in 5.9 per cent of the idiopathic group and in 45 per cent of the traumatic group. It can

48. Grant, F. C.: Ventriculography and Encephalography, Arch. Neurol. & Psychiat. **27**:1310 (June) 1932.

thus be noted that normal encephalograms, as well as ventricular asymmetry, predominate in the posttraumatic group.

Encephalograms are also of value in ruling out the presence of a tumor of the brain as the cause of epilepsy. In 2 cases under our observation epilepsy was a predominant symptom following a head injury. Later studies revealed the presence of a tumor of the brain, thus eliminating the preceding trauma as the cause of the epilepsy.

Fig. 3.—Roentgenogram showing posttraumatic epilepsy with inequality of the size of the ventricles and cortical atrophy.

For medicolegal purposes the encephalogram has only suggestive value in the differentiation of posttraumatic from idiopathic epilepsy. No definite statement can be made.

THERAPEUTICS

It is not within the scope of this paper to enter into a discussion of the therapeutics of epilepsy. However, two methods may be mentioned:

(1) the operative excision in cases of focal epilepsy, as described by Foerster and Penfield, and (2) encephalography for its therapeutic value. Grant, in reporting 51 cases of traumatic epilepsy, the progress of which in regard to convulsions has been followed from twelve months to two years, reported 12 in which the patient was completely relieved, 10 in which the patient was partially relieved, 17 in which the patient was unimproved and 12 in which the outcome was fatal. In the 39 cases

Fig. 4.—Roentgenogram showing posttraumatic epilepsy with a ventricular shift and cortical atrophy.

which he followed, 22, or 55.6 per cent, of the patients showed definite improvement; 17, or 43.5 per cent, showed no improvement. For this reason the question of encephalography, both as a differential diagnostic measure in distinguishing cases of an organic pathologic condition, such as tumor of the brain, from those of traumatic epilepsy and as a therapeutic measure, should be considered in cases of posttraumatic epilepsy. Similar results have been obtained by Fay, Pancoast, Pendergrass, Bingle and Glaser.

CONCLUSIONS

A statistical study of cases of head injury reveals a wide discrepancy in the percentage of incidence of generalized epilepsy following trauma of the head. A careful analysis of these articles from our own personal experience indicates that the most likely incidence is in the neighborhood of 2.5 per cent in the cases of more severe head injury.

A statistical study indicates that epilepsy does not develop after minor, but follows only severe, head injury and generally occurs only in cases in which there has been fracture of the skull.

Generalized epilepsy may develop within the first ten days after head injury, provided the injury is of excessive severity.

Posttraumatic epilepsy occurs most frequently from six months to two years after the injury, less frequently from two to seven years afterward and infrequently from seven to twenty years afterward.

In attributing the epilepsy to trauma, all extraneous factors must be ruled out, particularly a history of convulsions prior to the trauma. Thorough physical and neurologic examinations should be made in order to establish that there is no organic, physical or neurologic disease and no mental condition other than the effects of the trauma causing the convulsions. In cases in which the first convulsion occurs at the time of the injury, special care in getting a detailed history is necessary to make certain that the injury did not happen because of the onset of an attack of idiopathic epilepsy.

Convulsive seizures developing in the first six months after minor head injuries should be considered psychoneurotic in origin, and every effort should be made to rule out such an etiology before the condition is diagnosed as true epilepsy. These statistical studies and our case reports have indicated the psychoneurotic character of such seizures, particularly in the cases of minor head injury.

We know of no method of preventing the occurrence of generalized epilepsy following head trauma other than the utilization of the accepted methods of treatment of the original injury.

Unless there is some special contraindication, we believe that encephalograms should be made in every case of posttraumatic epilepsy, both because they may have definite therapeutic value and because they may give further information of marked value in outlining further advisable steps for treatment; in some cases they have shown evidence that open operation should be performed.

INJURIES TO THE CRUCIAL LIGAMENTS

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Injuries to the crucial ligaments have been considered among the more serious internal derangements of the knee joint, and a great deal of surgical thought and work has been directed toward obviating the ill effects of these injuries. At the outset, Mayo-Robson [1] and others attempted simple suture of the torn ligament. Later silk, then wire and finally fascia wrapped about silk were used to replace the torn ligament. However, Sir Robert Jones called attention to the fact that in complete dislocations of the knee, rupture of both crucial ligaments had to be predicated, and he expressed the opinion that the good results, when present, were due to the effects of prolonged rest rather than to the repair of the torn ligaments. In 1917, Hey Groves [2] published the description of his operation for the reconstruction of the ruptured anterior crucial ligaments. Though it effected a great improvement of the surgical results, the operation did not appear to be entirely satisfactory until its modification by the addition of the Alwyn Smith [3] procedure, which was designed for the repair of the tibial collateral ligament and which later was accepted by Hey Groves.[4] This combined operation has given some excellent results in my hands, as well as in the hands of other surgeons. The main drawback has been that the operation is complicated and requires considerable technical skill. This, taken in conjunction with other considerations, which will be noted later, has led to a review of the subject, particularly with the view of determining whether the disability is due entirely to injury of the crucial ligament and whether, in that event, the Groves-Smith operation is the method of necessity.

In spite of much that has been written about the functions of the crucial ligaments, there is still far from unanimity of opinion on the subject. From a consideration of the size and strength of the crucial ligaments, it appears reasonable to infer that they develop in response to powerful stresses and strains and that they perform a valuable and necessary rôle in the economy of the knee joint. But just what this rôle may be is problematic. Some investigators think that the crucial ligaments act merely as ligamenta teres, binding the tibia and femur

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From the service of Dr. Harry Finkelstein at the Hospital for Joint Diseases.

1. Mayo-Robson, A. W.: Ann. Surg. **37**:716, 1903.
2. Groves, E. W. H.: Lancet **2**:674 (Nov. 3) 1917.
3. Smith, Alwyn: Brit. J. Surg. **6**:176, 1918.
4. Groves, E. W. H.: British J. Surg. **7**:505 (April) 1920.

together, and others consider that they are the true posterior ligaments of the knee joint, while still others believe that they represent the vestiges of ligaments which originally united two separate tibiofemoral joints. The majority, however, are of the opinion that these ligaments are the main, if not the sole, means of maintaining the stability of the joint. Since it is on the question of the significance of these ligaments that the rationale of the surgical therapy depends, a brief résumé of the knowledge on this subject will be condoned.

Information as to the function of the crucial ligaments has been gained through three main sources: (1) the study of their anatomic configuration and apparent physiologic action in the cadaver; (2) the experimental production on the cadaver of injuries to one or more of the ligaments of the knee joint and the determination of the disabilities so occasioned, and (3) the clinical study of patients.

Anatomically, by the obliquity of their direction, the crucial ligaments seem specifically designed to prevent displacement of the tibia in an anteroposterior direction. The anterior crucial ligament, attached above to the outer condyle of the femur and running downward, forward and medially to the depression in front of the tibial spine, appears to act as a check to forward displacement of the tibia. The posterior crucial ligament, coursing downward, backward and laterally from its attachment on the inner femoral condyle, appears to function as a check to backward dislocation of the tibia. Since forward tibial displacement normally occurs during extension and backward displacement during flexion, it has been believed that the anterior crucial ligament is tense only during extension while the posterior crucial ligament is tense only during flexion. The more careful studies of Weber,[5] Meyer,[6] Fick[7] and others have demonstrated that this is far from the truth.

It appears that, in its normal function, motion of the knee may be divided into two components; a flexion-extension motion, which occurs around a transverse axis, and a rotatory motion, which takes place mainly in extreme extension or in extreme flexion around a vertical axis. During the rotatory motion the crucial ligaments, acting together, prevent excessive internal rotation of the tibia, but neither plays a part in the absence of the other. This is due to the fact that during flexion the posterior crucial ligament acts as a stay around which the anterior winds and, thus becoming taut, hinders undue internal rotation of the

5. Weber, W. E., and Weber, E. F.: Mechanik der menschlichen Gewerkzeuge, Göttingen, Dieterich, 1836; quoted by Fick[7] and Pagenstecher.[8]

6. Meyer, G. H.: Die Statik und Mechanik der Gelenke, Leipzig, Wilhelm Engelmann, 1873, p. 368.

7. Fick, R.: Anatomie und Mechanik der Gelenke, in Bardeleben, K. H.: Handbuch der Anatomie, Jena, Gustav Fischer, 1904, p. 521.

tibia on the femur. During the act of normal flexion and extension, parts of both crucial ligaments are tense throughout the movement, different parts becoming taut during different states of the motion, as may be gathered from the table devised by Fick.

In hyperextension, too, the anterior crucial ligament given herewith was found to be taut. It was found that in the alternation between flexion and extension the position of maximum tension on both crucial ligaments was that of flexion and internal rotation of the tibia on the femur. From these considerations it appears reasonable to conclude that the crucial ligaments function mainly during the act of flexion and that during extension the support of the knee is undertaken by other structures, viz., the collateral ligaments and the muscles about the joint.

In the main these anatomic findings have been substantiated by the evidence obtained through experimentation on the cadaver. Weber [5] showed that if the collateral ligaments of the knee remain intact and the crucial ligaments are cut, the knee retains its stability in extension. In

Tension of the Crucial Ligaments

	Fibers	Extension	Midposition	Flexion
Anterior	Anterior	Taut	Taut	Relaxed
	Posterior	Relaxed	Relaxed	Taut
Posterior	Anterior	Relaxed	Taut	Taut
	Posterior	Taut	Relaxed	Relaxed

flexion, however, the knee becomes unstable in the same sense as that if the anterior crucial ligament alone is cut the tibia can be displaced forward while if the posterior crucial ligament is cut backward displacement of the tibia becomes possible. On the other hand, if the crucial ligaments remain intact while only the collateral ligaments are cut, the stability of the knee is preserved during flexion but lost during extension. Pagenstecher [8] showed that with the knee flexed over a bolster rupture of the anterior crucial ligament results when the head of the tibia, struck from behind, is driven forward, while a rupture of the posterior crucial ligament occurs when the blow is delivered in front. Honigschmied [9] demonstrated the following facts: 1. Hyperextension of the knee results in injury to the tibial collateral ligament. However, he cited two cases reported by Stark in which rupture of the crucial ligaments occurred. If extension is continued after this first the anterior and then the posterior crucial ligament is ruptured. 2. Hyperflexion of the knee is normally impossible because of the interposition of the soft tissues. If a wedge is placed behind the knee, hyperflexion over this bolster brings about tearing of the anterior crucial ligament. 3. Hyper-

8. Pagenstecher: Deutsche med. Wchnschr. **29**:872, 1903.
9. Honigschmied, J.: Deutsche Ztschr. f. Chir. **36**:587, 1893.

adduction or hyperabduction of the tibia results in injury to the crucial ligaments only after preliminary tearing of the collateral ligaments. 4. Hyperpronation, i. e., internal rotation of the tibia, and hypersupination, i. e., external rotation of the tibia, occasion damage to the capsule, the collateral ligaments or the menisci before causing lesions of the crucial ligaments. Pringle [10] succeeded in tearing the anterior crucial ligament by fixing the pelvis and then flexing, abducting and internally rotating the leg at the knee. He then noted that in such cases he "always found a degree of tearing of the internal lateral ligament at its deep or articular aspect; it never was complete; that is to say, it never involved the superficial fibers and none of the other ligaments of the joint showed any degree of injury. With the short fibers of the internal lateral ligament ruptured, it is not only possible but probable that a greater degree of abduction would be permitted than if they were intact."

As a consequence of these observations, two tests have been devised, which were believed to reveal injuries of the anterior crucial ligament [11] and which were believed to render the establishing of a diagnosis of rupture of this ligament an elementary matter. The first of these, the extension test, based on the experiments of Pagenstecher, Honigschmied and Pringle, is described by Jones and Smith [12] in the following words: "If, after an injury to the knee, the tibia can be displaced backwards or forward or rotated inward in the extended position, an injury to one or both crucial ligaments may be diagnosed." This statement is in complete contradiction of Weber's experiments and can be reconciled with clinical experience only if it is admitted categorically that every injury to either of the crucial ligaments is invariably associated with injury to the collateral ligaments. This, of course, is not the case. There is no doubt that isolated injuries to either the collateral or the crucial ligaments may occur. In the typical case, injury to the collateral ligaments can readily be diagnosed by the demonstration of abnormal lateral mobility with the knee in extension. The difficulty in diagnosis arises when lesions of both structures are present. In some instances only lateral instability, the characteristic sign of injury to the collateral ligament, is found, as will be seen from a study of the two cases reported by Pringle. In both, the erroneous diagnosis of rupture of the internal lateral ligament was made, but at operation an avulsion of the medial tibial spine was found in one case and a tear of the anterior crucial ligament in the other. In neither of these cases was

10. Pringle, J. Hogarth: Ann. Surg. **46**:169, 1907.

11. Because of the relative rarity of injuries to the posterior crucial ligament, the majority of commentators confine themselves to discussions of injuries to the anterior crucial ligament.

12. Jones, R., and Smith, A.: Brit. J. Surg. **1**:70, 1913.

there a rupture of the superficial fibers, but it was presumed that the deep fibers of the lateral ligament were involved. There was slight anteroposterior mobility in the second case during the anesthesia. The good results of simple suture in these cases can be explained only on the assumption that satisfactory healing of the lateral ligaments had occurred. Instead of demonstrating the presence of injury to the crucial ligaments, this test establishes conclusively only the additional loss of integrity of the tibial collateral ligament. The insistence of many surgeons that in the absence of a positive reaction to the extension test surgical intervention is contraindicated appears to be well grounded in the sense that only the patients who give a positive reaction show a degree of disability due to lateral instability sufficient to justify operation.

The second of the two tests, a fixation test, is characterized by the *signe de tiroir* of Rocher, or what may be purposely miscalled the "rocker" sign. It is elicited by fixing the foot with the knee in flexion. The upper end of the leg is grasped, and it will then be noted that in the event of a tear of the posterior crucial ligament the head of the tibia can be displaced abnormally forward. When the results are positive, this test is reliable, especially in cases in which a history of trauma has been obtained. Unfortunately, the sign is reputed to have been present in only one of about eight cases in which at operation ruptures of the crucial ligament have been found. All who have had the opportunity of operating on many knee joints have undoubtedly had the unpleasant experience of discovering lesions of this sort which were not suspected before arthrotomy because of the complete lack of symptoms of either anteroposterior or lateral hypermobility. In one case in which operation was performed recently the patient presented symptoms, such as locking, that were suggestive of an injury to the medial semilunar cartilage, but there was no evidence of preternatural mobility.

REPORT OF CASES

CASE 1.—*Repair of the anterior crucial and tibial collateral ligaments by the method of Hey Groves and Smith.*

L. S., a woman, aged 42, was admitted to the hospital on Jan. 19, 1932. There was a history of rheumatism twenty years previously, with repeated giving-way of one knee, associated with locking. About twelve days before admission to the hospital, the patient twisted her knee; she had since complained of pain, swelling and limitation of both flexion and extension. There was a moderate effusion into the joint, with a slightly positive "rocker" sign. In the extended position the knee was stable in all directions. There was definite tenderness over the anterior horn of the medial semilunar cartilage, with accentuation of pain on extension of the knee. The roentgen examination was reported as giving negative results. This, in conjunction with the aforementioned signs and symptoms, led to a diagnosis of fracture of the semilunar cartilage, for which operation was advised.

On January 21 the joint was opened through a median parapatellar incision. After evacuation of a moderate amount of fibrin-flaked fluid, it was noted that the anterior crucial ligament was torn from its tibial insertion and was so frayed that suture was impossible. A typical operation by the method of Hey Groves and Smith was performed. The fascial graft for the repair of the tibial collateral ligament was accurately placed over the anterior portion of the internal lateral ligament and was drawn particularly taut by gentle forcing of the leg into adduction. The wound was closed, and a plaster of paris bandage cast applied, with the knee in slight flexion. The patient pursued an uneventful postoperative course, and the leg was released from the cast at the end of about six weeks. She immediately complained that there was something "awfully tight" about the inner aspect of the knee which interfered with flexion. Physical therapy was started, and a knee-cage brace applied. Within a relatively short time the range of flexion gradually began to increase, so that at the present time the patient is able to bend the knee to slightly beyond a right angle. The power of extension is complete, and the patient has never since noted any instability or symptoms of giving way or locking of the joint.

A somewhat similar situation has been observed in cases of avulsion of the internal tibial spine. In uncomplicated cases, in which concomitant tearing loose of the anterior crucial ligament is almost invariably found, the "rocker" sign is negative, and diagnosis is impossible, except by noting the development of the symptom of bone block or by the study of the roentgenogram. Taylor [13] reported a case in which a pyriform osteoma, 3 by 5 by 7 cm., was disclosed by the roentgenogram. At operation, "there was a small sesamoid bone attached by a ligamentous band to the posterior extremity of this large osteoma. This ligamentous band was evidently the anterior crucial ligament, which had been torn loose from its tibial attachment, and in it the osteoma developed." This patient apparently suffered no symptoms from the tearing of the crucial ligament and suffered none after its removal. But for the limitation of extension, due to the gradual increase in the size of the intra-articular mass, undoubtedly derived from the avulsed tibial spine, the patient might never have become aware of any difficulty. The following case is fairly typical of this type of injury.

CASE 2.—*Suture of the anterior crucial ligament.*

V. R. was seen on March 4, 1930, more than six weeks after he had fallen about 12 feet (3.6 meters), landing on his feet and then falling forward and striking the flexed right knee. Immediately after the accident he complained of severe pain and inability to extend the knee or to bear his weight. A roentgenogram taken shortly afterward showed a "fracture of the knee joint," and a posterior splint was applied for one week. At the end of this time the patient was unable to walk, and aspiration of the knee, baking and massage were instituted, without any improvement. When first seen the patient walked with a marked limp. The knee joint was moderately distended by fluid and could not be completely extended (extension was possible to 170 degrees; flexion, to 70 degrees). There was no hypermobility in the anteroposterior or lateral direction, either in the extended

13. Taylor, R. Tunstall: Ann. Surg. **37**:84, 1903.

or in the flexed position of the leg. Roentgenograms showed "a complete fracture of the medial crucial spine, with slight rotation and anterior displacement of the fragment."

On March 6 arthrotomy was performed through a median parapatellar incision. The intercondylar space was filled with a thick pannus; the synovial membrane was thickened and congested; the medial crucial spine and the anterior crucial ligament were found to be torn from the tibial insertion and adherent to the granulation tissue in the intercondylar space. The bone fragment was pried loose from this mass and was then detached from the lower end of the anterior crucial ligament, which with great difficulty was sutured to the head of the tibia. With the patient under anesthesia there was a suggestion of a positive "rocker" sign, but this had completely disappeared by the time motion of the knee was started. On March 25 the patient was permitted to be up and about; there was apparent good stability in the knee joint. In view of the early motion and the relatively insecure suture of the crucial ligament, no great hope for its functional restoration was held. On April 2 the patient was discharged from the hospital with perfect stability and a normal range of painless motion.

In these cases, as in several others, an observation was made which may be of value in throwing light on the relatively low incidence of positive results in the application of a test a positive reaction to which has been considered pathognomonic of injury to the crucial ligament. In the first place, it was noted that in cases in which the patient gave negative reactions to the test before operation, a "rocker" sign might be obtained when the patient was under anesthesia. At first this was noted with a keen sense of chagrin; it was considered to indicate carelessness in the examination. However, when this phenomenon was observed repeatedly, even after particular attention had been paid to the presence of the sign, it was realized that the anesthetic relaxation of the patient had entirely altered the condition under which the two tests were made. When the tone of the quadriceps and the other muscles which control the action of the knee had been abolished, it was possible to demonstrate excessive anterior mobility of the flexed knee. The prompt disappearance of this sign on the resumption of active motion and the reestablishment of the normal tone of the muscles led to the belief that the quadriceps extensor played an important rôle in the elicitation of the "rocker" sign. In case 3, to be reported, the patient had developed such control over his muscles that he was able voluntarily to project or retract the lower end of the femur on the fixed, flexed leg.

In cases of hypotonia [14] due to repeated effusion in the joint or to dysfunction of the parathyroid mechanism it is known that such relaxation of the muscular and ligamentous structures may occur. The significance of this factor in the evaluation of the rocker sign has been overlooked, though its value in the treatment of the underlying condition

14. Finkelstein, H.: Joint Hypotonia, New York M. J. **104**:942 (Nov. 11) 1916.

seems to have been amply appreciated. Timbrell Fisher [15] stated that "the most important factor in the treatment is so to build up the quadriceps extensor that they compensate, to a certain extent, for the weakness and instability caused by the loss of the action of the crucial ligament. In at least two cases, in which complete rupture of the anterior crucial was found at operation by the author, attention to this principle has enabled the patients to continue playing strenuous football." For my part, I have been led to feel that this is true only in

Fig. 1.—Anteroposterior roentgenogram showing a sprain fracture of the medial femoral condyle at the insertion of the tibial collateral ligament and a sprain fracture of the medial tibial spine at the insertion of the anterior crucial ligament.

instances in which no associated injury to the internal lateral ligament is found. In such cases, the extension test has invariably been negative, while the "rocker" test has or has not been positive, depending on the degree of tone in the quadriceps muscle. But in cases in which an injury to the internal lateral ligament has been superadded to the injury to the crucial ligament, the reactions to both tests has been found to

15. Fisher, A. G. Timbrell: Internal Derangements of the Knee Joint, ed. 2, New York, The Macmillan Company, 1933, p. 171.

be positive, regardless of the power of the quadriceps, and this can be explained only on the basis of the additional injury. Most frequently the word of the examining physician as to the true state of affairs, especially as regards the lateral ligaments, must be accepted without any other affirmation. In one patient who is at present under observation but who has not yet consented to operation it was possible to obtain roentgenographic evidence (fig. 1) of the tearing away of both the crucial ligament and the tibial collateral ligament. The feeling that the major part of the disability in such cases is due to the insufficiency of the lateral ligament has been confirmed by the study of the following cases.

Fig. 2 (case 3).—Photograph showing abduction of the knee, with separation of the medial femoral and tibial condyles, due to rupture of the tibial collateral ligament.

CASE 3.—*Reconstruction of the anterior crucial and internal lateral ligaments by the method of Hey Groves and Smith.*

W. S., a man, aged 26, was admitted to the hospital on Nov. 18, 1929; his left knee had been run over by an automobile one year before. The only treatment had consisted in a two weeks' period of hospitalization in a midwestern institution. Since that time he had noted marked instability in the knee, with a tendency to dislocation on going up or down stairs. There was no history of locking. It was noted that "in spite of the rather serious nature of the injury, the patient is still able to walk fairly comfortably and with a fair degree of stability. This stability is largely maintained by the action of the hamstrings and the quadriceps muscles. When seated, the patient can project the lower end of the femur backward and forward on the tibia and can rotate the femur externally." There was

a typical "rocker" sign with the knee flexed, and with the knee extended, external rotation of the leg, hyperextension of 5 degrees, abnormal backward and forward displacement and abduction of 10 degrees were possible (fig. 2). The roentgenogram showed a "small calcific body, perhaps a detached crucial spine, in the knee joint." A diagnosis of rupture of both crucial ligaments and the tibial collateral ligament was made, and operation was advised.

Arthrotomy, performed on November 21, disclosed absence of the anterior crucial ligament. The stump of the posterior crucial ligament was found in the depression behind the crucial spine. The tibial collateral ligament was torn, and the medial semilunar cartilage was detached. The semilunar cartilage was resected, and a typical Hey Groves-Smith reconstruction was performed, special attention being paid to the repair of the internal lateral ligament. It was noticed on the operating table that when repair of the internal ligament had been completed, practically complete stability of the knee joint was restored. After closure of the wound, a plaster of paris bandage cast was applied, with the knee in extension. On Jan. 27, 1930, the cast was removed, a knee-cage brace was fitted, and active motion was begun. By February 24, extension of the knee to 180 degrees and flexion to 115 degrees were possible. By April 28 flexion had increased to 90 degrees, and the patient could run or hop upstairs, bearing his weight normally on the leg on which operation had been performed. There was no evidence of anteroposterior mobility, but there was a slight degree of lateral mobility, which did not interfere with the function of the knee. Thereafter the patient was lost sight of.

This case is of special interest, because of the presence of injury to the posterior crucial ligament. Since some authors claim that the posterior crucial ligament is of the greatest importance in maintaining the stability of the knee, it would be of great value to be able to determine this point in a case in which repair of this ligament had been purposely neglected. However, the fact that there was a slight degree of lateral instability inclines me to the opinion that the instability was occasioned either by insufficient tension on the fascial graft at the time of the operation or by relaxation of the graft subsequent to the beginning of active motion.

CASE 4.—*Hey Groves reconstruction of the anterior crucial ligament.*

F. L., a man, aged 38, was first seen in May 1930. He was a printing press rigger and in the course of his work had been injured by a piece of machinery which fell on his right side. He was taken in an unconscious condition to a nearby hospital, where a diagnosis of fracture of the pelvis, probable fracture of the ribs and an internal derangement of the right knee was made. He remained at the hospital for about three months. On his discharge he noted swelling of the knee. He returned to his work, but was forced to discontinue it because of recurrent swellings, occasional giving way and a sensation as of something clicking on the inner aspect of the knee.

He walked fairly well but with a marked limp. The knee was distended by fluid, and there was tenderness on pressure over the anterior horn of the internal semilunar cartilage, as well as over the internal lateral ligament. There was no lateral hypermobility, but with the knee in flexion there was a definite "rocker" sign. A tentative diagnosis of fracture of the semilunar cartilage with rupture

of the anterior crucial ligament was made, and operation was recommended. This was undertaken on May 15, through a median parapatellar incision. The anterior crucial ligament was found torn away from its femoral attachment and rolled on itself. The posterior crucial ligament was frayed and attached by only a few fibers. The semilunar cartilage was normal. A Hey Groves operation without the Smith modification, because of the absence of signs of lateral mobility, was carried out. The cartilage was left in situ, and the leg was encased in plaster of paris after closure of the wound. By June 21, on removal of the cast, the patient could passively flex the knee to a right angle. In this position there was no sign of abnormal anteroposterior mobility. A knee-cage brace was applied, and active motion was begun. The patient was discharged from the hospital on July 12, walking, and was thereafter given physical therapy. In September he resumed

Fig. 3 (case 4).—Photograph showing the postoperative state. The patient's ability to bear weight in the partly flexed position, in the act of ascending the stairs, is seen.

his work. However, in October he again returned to me with a swollen knee, and in December there had been a return of the anteroposterior mobility previously noted. He was given rest and physical therapy, with marked improvement. In February 1931, he returned to his usual work and was then lost sight of until June, when he was again examined. At that time there was no lateral mobility and there was still slight anteroposterior mobility, but the musculature had so strengthened that the patient could perform his work, using his knee in a perfectly normal manner (fig. 3).

CASE 5.—*Resection of the anterior crucial ligament and medial semilunar cartilage.*

M. K., a man, aged 31, was seen on Oct. 4, 1933, with a history of having injured the left knee while playing Gaelic football one year previously. He

jumped to catch the ball and landed on his feet, with the left leg abducted and externally rotated and with the thigh adducted. He was unable to extend the leg until some friends "pulled the leg out," when he felt something slip into place. Though he attempted to continue the game, the swelling and pain were so severe that he was forced to desist. He remained in bed for four days, after which the symptoms had so far receded that he thought that he was well, though he admitted that he had a sensation of weakness in going up or down stairs. After several months the patient resumed his playing of football, with exactly similar consequences. Several months after this attack he again attempted to carry on his professional football career, with recurrence of the symptoms. Since this last episode the patient had noticed that whenever he twisted suddenly "something seemed to slip out of place in the left knee," which then became locked in flexion.

Examination disclosed that the patient walked without a limp. There was no fluid in the knee joint, no crepitus on motion and no abnormal mobility, either anteroposteriorly or laterally. There was slight swelling over the postpatellar fat pads, with an obliteration of the parapatellar depressions. There was definite tenderness over the anterior horn of the medial semilunar cartilage, with accentuation of tenderness on extension of the leg. A diagnosis of fracture of the medial semilunar cartilage was made, and operation was advised. Arthrotomy, performed on Nov. 8, 1933, showed a moderate increase in synovial fluid and marked congestion, with thickening of the entire synovial membranes and of the semilunar fat pads. The internal semilunar cartilage was found shrunken. The crescentic free edge was blunted, and its posterior part was torn half through. The anterior crucial ligament was torn away from its femoral attachment, and the free edge was frayed, as if it had been crushed between the femoral and tibial condyles. With the patient under anesthesia a positive "rocker" sign could readily be demonstrated. The cartilage was resected, along with the damaged portion of the postpatellar fat pad. The stump of the crucial ligament was cut away from its tibial insertion, and the wound was closed in the usual manner. The pathologic specimen was reported as showing in the cartilage "a tendency to fibre out," in the shreds of the crucial ligament "a very marked myxoid degeneration, with proliferating cartilage cells in some areas" and in the synovial tissue "villous hypertrophy and round cell infiltration." On the patient's discharge from the hospital he was able to extend the knee completely and to flex it to about 90 degrees. There was no evidence of abnormal mobility either in the anteroposterior or in the lateral direction.

CASE 6.—*Resection of the anterior crucial ligament and medial meniscus.*

P. C., a man, aged 42, was seen on April 3, 1934, with a history of having fallen on the flexed and abducted right knee more than six weeks previously. Immediately after the accident, on attempting to arise, the patient noted a click on the inner aspect of the knee; he was unable to straighten his leg. Within a short time the knee became markedly swollen, and he was forced to discontinue his work. His physician advised hot compresses and diathermia, but there was no relief. Since then the patient had noted locking of the knee at least once daily and a marked sense of insecurity in going up or down stairs. On examination he walked with a definite limp and was unable to bring the heel to the floor because of the flexion at the knee joint. The knee was slightly enlarged, contained a slightly increased amount of fluid and gave a definite patellar ballottement. Extension was possible to 140 degrees and flexion to 90 degrees. There was tenderness over the anterior horn of the medial semilunar cartilage, with accentuation of the tenderness on extension of the leg. A slight degree of abnormal mobil-

ity could be demonstrated both in the anteroposterior and in the lateral direction. This observation could not be accurately evaluated because the knee could not be brought into full extension. However, a tentative diagnosis of bucket-handle fracture of the semilunar cartilage, with the possibility of an injury to the anterior crucial ligament, was made, and arthrotomy was advised. The joint was opened through a small vertical median parapatellar incision. A typical bucket-handle fracture of the medial semilunar cartilage was observed, as well as a tearing away of the anterior crucial ligament from its tibial attachment. The cartilage was resected. This permitted complete extension of the knee, when it was observed that there was no lateral mobility. It was consequently believed that the lateral mobility previously observed was apparent and was due to the fact that the knee could not be properly extended. The anterior crucial ligament was thereupon resected, and the knee was closed in the usual manner, without immobilization. Motion was started as soon as the postoperative pain had disappeared. There was no evidence of abnormal anteroposterior mobility. Walking was permitted on the tenth day, just before the patient's discharge from the hospital. Within three weeks of his operation the patient was able to flex the knee beyond a right angle and to extend the leg completely. There was no instability. The patient could use his knee normally, and after an additional period of four weeks of physical therapy he returned to his regular work. Subsequently marked lateral instability of the knee, which was not improved by exercise, support, etc., developed; a Smith repair of the tibial collateral ligament was advised.

CASE 7.—*Smith reconstruction of the internal lateral ligament for rupture of the anterior crucial and the internal lateral ligament.*

B. G., a woman, aged 26, was seen in January 1934, with a history of having fallen on her flexed right knee more than nine years before. After a short period of treatment the swelling and disability disappeared, and the patient was able to resume her usual activities. She noted, however, that when she was swimming her knee occasionally locked and that there was a sense of insecurity in going up or downstairs. In July 1933 she had jumped off a low bulkhead and had landed on her partly flexed knee; she had then fallen backward and twisted the knee. She immediately complained of severe pain and inability to bear her weight, because of giving way of the knee. She was treated conservatively by means of a cast and physical therapy, with some relief, though complete extension of the leg was impossible. Roentgen examination showed no evidence of fracture. There was marked atrophy of the left thigh. There was no fluid in the knee joint or crepitus on motion. Extension was possible to about 175 degrees. Flexion was normal. In extension there was a slight degree of abnormal adductibility. In flexion the tibia could be displaced forward on the femur. There was definite tenderness over the tibial insertion of the tibial collateral ligament, and slight tenderness was noted over the anterior horn of the medial meniscus, with accentuation of the pain on extension. It was felt that the patient was suffering from a lesion of the medial meniscus and a relaxation of the internal lateral ligament, with possibly a tear of the anterior crucial ligament. Operation was suggested.

The patient entered the hospital on February 5, and arthrotomy was performed several days later. With the patient under anesthesia, it was remarked that with the leg both in flexion and in extension there was marked lateral, as well as anteroposterior, mobility. When the joint was opened, the medial meniscus was found to be loose. There was an erosion of the cartilage on the inferior surface of the medial femoral condyle. The anterior crucial ligament was diligently sought for, but it could not be found. It was readily seen that the posterior crucial ligament

was normal. The cartilage was resected. Two tunnels were then drilled in the coronal plane through the lower end of the femur and the upper end of the tibia. A long strip of fascia lata was freed subcutaneously, being left attached at its lower end. The upper end of the fascial graft was then passed through the femoral bone tunnel from without inward and was sutured to the periosteum both at its entrance and at its exit from the bone. It was then passed down the inner aspect of the knee in the plane of the anterior portion of the medial collateral ligament and with the leg in slight forced adduction was passed through the tibial tunnel from within outward, being again sutured to the periosteum at both extremities of the tunnel. Immediately after completion of this step of the operation it was observed that lateral stability had been completely restored but that anteroposterior mobility persisted. The wounds were closed, and a plaster of paris bandage cast was applied from the toes to the midthigh, with the knee in slight flexion. The leg was not dressed until March 28, at which time the wounds were found to be healed. There was moderate swelling of the knee, as was to be expected. Lateral motion was present in slight degree. About 20 degrees of active motion was possible. Under treatment with physical therapy, active and passive motion and the application of diathermia to the knee and sinusoidal current to the quadriceps muscle, the instability gradually disappeared, and the range of normal motion gradually increased, until by the middle of May extension to 180 degrees and flexion to 90 degrees were possible, without any evidence of either anteroposterior or lateral mobility.

The importance of the internal lateral ligament in maintaining the integrity of the knee joint is well attested by the following case.

CASE 8.—*Rupture of the anterior crucial and fibular collateral ligaments.*

Dr. M. F., a man, aged 24, was seen in July 1932. He had injured the knee one week previously. While he was wrestling on the beach, one of his comrades had fallen on top of the extended right knee and hyperextended it to the point at which a forward dislocation of the tibia on the femur had occurred. With some difficulty his friends reduced the dislocation by traction and the patient was taken home. At the time of the first examination the knee was still markedly swollen. The skin was ecchymotic well down in the leg, and there was a marked effusion into the articular space. The knee could be extended to 180 degrees and flexed to 90 degrees. In the flexed position there was slight anteroposterior motion, and in the extended position hyperadduction of about 15 degrees was possible. The internal ligament appeared to be intact. The roentgenogram showed a shadow suggestive of a sprain fracture of the medial tibial condyle. There was no interference with the circulation of the leg or evidence of injury to the posterior tibial or peroneal nerves.

It was considered that the patient had suffered a rupture of the posterior portion of the capsule, with a tear of the anterior crucial and fibular collateral ligaments. But in view of the fact that the internal lateral ligament was apparently not involved, it was felt that immobilization was unnecessary. A knee-cage brace was fitted, the outer border of the sole and heel of the shoe was elevated, and the patient was encouraged to make gentle, active use of the knee. Diathermia was begun as soon as the patient was able. After about six months, as soon as complete stability of the knee had returned, the knee-cage brace was discarded, and at the present time (1934) the patient is able to engage normally in sports without any trace of inconvenience. There is no weakness, and there is no suggestion of anteroposterior or lateral hypermobility in either the flexed or the extended position.

COMMENT

Though the opinions expressed here were arrived at independently, it must be admitted that they were held with great temerity until reference to the literature discovered that other surgeons had given utterance to the same beliefs at an earlier date and with much more assurance. Le Riche,[16] who resected the anterior crucial ligament with perfect functional result, is reported to have observed that "excision of the anterior crucial ligament is compatible with functional restoration of the joint and is always satisfactory." Tixier and de Rougemont,[17] in discussing the question of diagnosis, stated: "One must say the diagnosis of a lesion of the crucial ligaments is often impossible, but of secondary importance, while it is vital to determine especially a lesion of the lateral ligament." In considering the matter of therapy they said: "We consider that the repair of the crucial does not constitute the indispensable element of success. . . . There is one essential step; the repair of the lateral." Tavernier,[18] who was of the same opinion, wrote: "I am constrained to suppose that the laxity presupposes rupture of ligaments other than the anterior crucial—possibly especially certain of the deep fibres of the internal lateral ligament." In 1932 he[19] reported a case in which both crucial ligaments and the internal lateral ligament were torn and in which repair of the latter ligament alone led to the restoration of a thoroughly stable, normally functioning knee joint.

As a conclusion from these and the previously noted considerations, I have come to believe that, contrary to the general opinion, the anterior crucial ligament is not a vitally necessary structure and that its loss is thoroughly compatible with relatively normal function of the knee, that the diagnosis of rupture of this ligament alone is not as simple as it has been stated to be, that the tests which are reputed to reveal ruptures of the crucial ligament are in all probability indicative of injuries to both the crucial and the internal lateral ligament, that the disability is due primarily to the loss of integrity of the internal lateral ligament and that in consequence surgical efforts should be directed primarily toward the repair of the internal lateral ligament by means of the Alwyn Smith operation rather than to the repair of the crucial ligament by means of the Hey Groves procedure.

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16. Le Riche, R.: Lyon chir. **16**:461, 1916; J. de chir. **34**:1, 1929.
17. Tixier, L., and de Rougemont, J.: Rev. de chir., Paris **51**:589 (Oct.) 1932.
18. Tavernier, L.: Lyon chir. **16**:353, 1919.
19. Tavernier, L.: Lyon chir. **29**:610, 1932.

LYMPHOGRANULOMA INGUINALE

ITS RELATION TO STRICTURE OF THE RECTUM

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Although lymphogranuloma inguinale has been recognized by the medical profession in some form or other under various names for several decades and the pathogenesis as well as other features were carefully described by Durand, Nicolas and Favre [1] in 1913, it has been only during the past year or two that the American literature has contained any significant references to it. DeWolf and Van Cleve [2] were probably the first American authors to report observations on the disease. When one considers the number of cases described in various reports, lymphogranuloma is apparently rather common. During the year that we have devoted attention to the disease in the clinic of Washington University we have encountered twenty-three cases. Innumerable synonymous terms, such as tropical bubo, climatic bubo and venereal lymphadenitis, have been used to identify the disease. If any of them is superior to lymphogranuloma inguinale, the term venereal lymphogranuloma appears to be most applicable. Ives and Katz,[3] who reported the first case identified in St. Louis, called attention to the vast number of terms which have been attached to the disease.

PATHOGENESIS

The etiologic factor in the production of the disease is probably a virus which gains entrance through a tiny or unnoticed primary lesion on the genitals and is no doubt dependent on sexual contact for transmission. The incubation time as given by numerous observers is from ten days to three weeks, although in one of our cases it was definitely

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1. Durand, M.; Nicolas, J., and Favre, M.: Lymphogranuloma inguinale subaigu d'origine génitale probable, peutêtre vénérienne, Bull. et mém. Soc. méd. d. hôp. de Paris **35**:274, 1913.

2. DeWolf, H. F., and Van Cleve, J. V.: Lymphogranuloma Inguinale, J. A. M. A. **99**:1065 (Sept. 24) 1932.

3. Ives, George, and Katz, S. D.: Lymphogranuloma Inguinale, with Report of a Case, Weekly Bull. St. Louis M. Soc. **27**:197, 1932.

proved to be five weeks. The primary lesion is so small that it is seldom noticed by the patient. When visible it is a tiny ulcer or fissure. However, in one of our female patients as many as eight or ten tiny superficial ulcers were visible on all sides of the vagina near the outlet at the time of her initial visit, which was three weeks after the onset of swelling of the inguinal lymph nodes. The disease, in this country at least, is more common in the Negro race. In our series of twenty-three cases, 87 per cent of the patients were Negroes. An observation which has been universally noted is the tendency toward the production of inguinal adenitis in men and the production of rectal ulceration or strictures in women. Weiss,[4] of Strasbourg, is conducting an extensive study and survey of the disease, devoting particular attention to the relation of the disease to benign stricture of the rectum. Symptoms indicative of stricture may not be noted by the patient for six or eight years following the initial symptoms. The rectal lesion is more apt to be followed by stricture in Negro women than in men or in white women. The explanation of the tendency toward involvement of the lymph nodes in men and of the rectum in women has been discussed in detail by Barthels and Biberstein,[5] Jersild[6] and Semba[7] and has been reviewed recently by Bloom.[8] In men most of the lymphatics from the penis, where the primary lesion is most apt to occur, drain anteriorly into the lymph nodes of the groins. On the contrary, most of the lymphatics of the vagina, especially of the proximal and posterior portion of the vagina, drain posteriorly into the lymph nodes along the rectum. Because it is so difficult to demonstrate a prominent enlargement or involvement of these nodes, there is still some difficulty in explaining the pathogenesis of the rectal lesions. It is possible that as the lymph nodes along the rectum become involved the stasis of the lymphatic system in the rectal wall distal to the nodes produces edema which encourages invasion by the virus and possible secondary invasion by organisms. The tendency toward the production of excessive scar formation following injury or infection in the Negro may explain the

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4. Weiss, A. G.: Personal communication to the authors.

5. Barthels, C., and Biberstein, H.: Elephantiasis penis et scroti und Lymphogranulomatosis inguinalis, Beitr. z. klin. Chir. **152**:325, 1931.

6. Jersild, O.: Notice historique sur l'infiltration hyperplasique du rectum avec retrécissement fibreux et sur l'origine prétendue syphilitique de cette affection, Ann. de dermat. et syph. **7**:74, 1926; Elephantiasis genito-anorectatis, Dermat. Wchnschr. **96**:433, 1933.

7. Semba, Y.: Anatomische Untersuchungen über die Lymphgefässysteme des Rektum, mit besonderer Berücksichtigung der Metastasenbildung des Rektumkrebses, Arch. f. klin. Chir. **149**:336, 1928.

8. Bloom, D.: Strictures of the Rectum Due to Lymphogranuloma Inguinale, Surg., Gynec. & Obst. **58**:827, 1934.

greater incidence of stricture in Negro women as compared with white women. It is thought by some that contamination of the rectum from the infected discharge of the vagina may account for the involvement of the rectum. It would, however, be difficult to explain involvement of the rectum in man, which is occasionally noted, unless homosexuality is a factor. Sexual perversion and homosexuality have been emphasized by some (Coults and his associates [9]) as an important factor in the production of the disease in the rectum.

Various experiments have been resorted to in an effort to reproduce the disease, and it is significant that experimental transmission is perhaps more readily accomplished than in any other disease known. The reports of these experiments have recently been reviewed in the thorough and valuable report by H. N. Cole [10] and will not be discussed here. The disease has been successfully transmitted to white mice, guinea-pigs, rabbits, monkeys and man. Levaditi and his associates [11] have done or confirmed a great portion of the work on the transmission of the virus.

Attention should be called to the fact that absolute proof of the causation of benign stricture is still lacking, although all observers who have devoted any attention to this phase of the disease are convinced that the greater portion (perhaps 90 per cent or more) of benign strictures of the rectum are due to lymphogranuloma inguinale. The positive Frei test obtained in association with these strictures is probably the most reliable evidence that rectal stricture is a part of the disease. However, we have observed at least one patient (no. 8, table 3) in whom a stricture of the rectum developed when only edema and ulceration were observed on the first examination. In this instance rectal symptoms, including chiefly tenesmus and the occurrence of blood and pus in the stool, were first noted by the patient in 1927. In 1931, when first seen by us, she had ulceration and edema of the rectum without narrowing of the lumen. One year later it was noted that a stricture was forming, and in 1934 the scar tissue was densely deposited on all sides of the rectum so that it barely admitted the tip of the index finger.

The fact that the Frei test is positive in these cases of rectal stricture added to the observation just noted convinces us that rectal stricture is

9. Coults, W. E.; Herrera, J. M., and Perroni, F. L.: Lymphogranulomatosis Venerea, Am. J. Surg. **21**:96, 1933.

10. Cole, H. N.: Lymphogranuloma Inguinale, the Fourth Venereal Disease, J. A. M. A. **101**:1069 (Sept. 30) 1933.

11. Levaditi, C.; Ravaut, P., and Schoen, R.: Propriétés virulicides du sérum des sujets atteints de lymphogranulomatose inguinale, Compt. rend. Soc. de biol. **109**:1267, 1932.

a part of the disease. In our hands the Frei test [12] has been remarkably specific. Every patient in our series who exhibited a positive Frei reaction was afflicted with one of the three major manifestations, namely, inguinal adenitis, ulcerative proctitis or rectal stricture.

The antigen is made by aspirating pus under sterile precautions from the groin of a person known to have the disease and diluting the pus with sterile physiologic solution of sodium chloride in a proportion of 1 to 4 or 1 to 2 depending on the thickness of the pus. It is sterilized by heating in a water bath at 60 C. for two hours one day and heating at 60 C. for an hour a day or two later. Obviously if culture of the antigen reveals bacterial growth false positive reactions will be obtained. The dose is 0.1 cc. intradermally. The typical reaction is an induration at the site of the injection which is at its maximum in forty-eight hours and may measure from 1 to 2 cm. in diameter. This area may be tender and is usually surrounded by an areola of redness. The test should be positive after the disease has been present for ten days or more, and in our experience the test remains positive as long as twelve to fifteen years after the onset of the disease. Usually, however, patients with an acute form give a stronger reaction. If when the disease is strongly suspected a negative or doubtful reaction is obtained, the test should be repeated. The incidence of a positive Wassermann or Kahn reaction in patients with rectal stricture, as noted in table 1 (28.5 per cent), seems entirely too small to admit the possibility of syphilis as being an important factor in the cause of stricture of the rectum. This incidence is no greater than the incidence noted in any other group of patients of the same social status. Of the fifteen patients with rectal stricture observed in our clinic during the past year, all except one gave a positive reaction to the Frei test. The patient with the negative reaction had a condition which had been diagnosed as one of the rare instances of rectal stricture occurring with idiopathic colitis. The extent of involvement of the colon in this case offered a contrast to the confinement of the disease to the terminal portion in lymphogranuloma inguinale. We conducted Frei tests on numerous patients with variable diagnoses, including syphilis, tuberculosis of the inguinal and cervical lymph nodes, granuloma inguinale and fistula in ano, but in every instance the reaction was negative. The fact that every one of these tests was negative is perhaps accidental, because in another series one might expect to encounter patients (especially men) who had had lymphogranuloma inguinale but recovered without residual symptoms.

12. Frei, W.: Eine neue Hautreaktion bei Lymphogranuloma inguinale, Klin. Wchnschr. **42**:2148, 1925.

Attention should be called to the fact that numerous observers have reported false positive Wassermann or Kahn reactions in cases of lymphogranuloma inguinale. We have one patient under observation a woman (patient 19, table 3) with definite evidence of acute lymphogranuloma inguinale whose reaction to the Kahn test was positive and remained so after thorough antisyphilitic treatment. The fact that she is young (26 years) seems to minimize the possibility that she has "Kahn-fast syphilis."

CLINICAL MANIFESTATIONS

In men the development of inguinal adenitis occurs in practically every instance. The swelling is usually bilateral and begins insidiously (the primary lesion is rarely observed by the patient) from ten days to

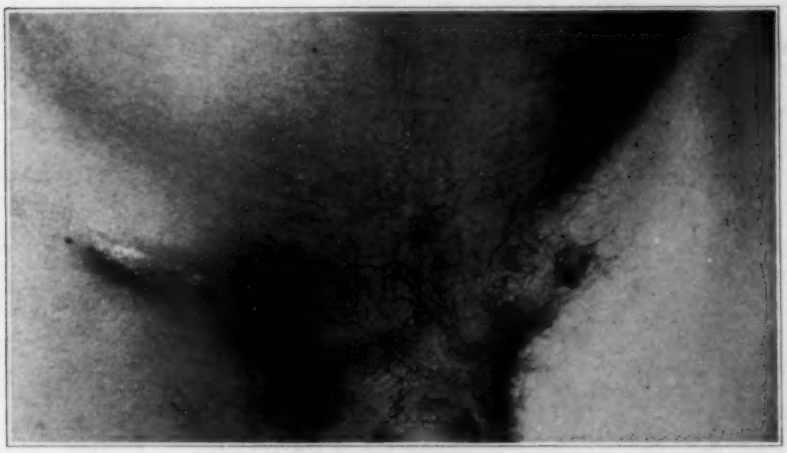

Fig. 1.—A Negro man with involvement of the inguinal lymph nodes on each side. The sinus present on the right was recent (of two or three weeks' duration) and resulted from the rupture of a small abscess of a lymph node to the exterior.

five weeks following exposure. Tenderness and pain are usually absent at first but may be present several weeks after the nodes become involved. Formation of an abscess with fluctuation usually occurs, but the amount of time required for its development is variable. Once fluctuation develops the abscess invariably breaks through the skin unless the pus is evacuated by incision or aspiration. In one of our cases aspiration of an abscess of an inguinal lymph node resulted in a cure as far as the local lesion was concerned. On rare occasions the suppuration of the nodes may subside and the sinuses close from six to eight weeks after the onset of swelling. As a rule, however, the sinuses and enlargement of the lymph nodes persist for many months. Ulcerative proctitis, which occurs in probably more than 75 per cent

of the women but in not more than 25 per cent of the men, may also be insidious in its development, although the presence of blood, pus and mucus in the stool is almost always detected by observing the patient shortly after the onset. Tenesmus and diarrhea may be present, although constipation may be very annoying when the formation of the stricture begins. Obviously, after the stricture becomes pronounced a loose watery stool is the only kind that the patient can pass. Multiple fistulas are not uncommon. Various types of condylomatous and granulomatous masses are observed about the anus. Sinus tracts and scarring about the vulva and anus are likewise commonly reported, but they were not seen frequently in our series.

As previously stated, when inguinal adenitis is the only manifestation of the disease there is rarely any permanent damage. Figures are not available as to the incidence of stricture following ulcerative proctitis, but the incidence is probably extremely high in Negro women if the disease is untreated, but low in men. On a few occasions ulcerative proctitis has been known to develop years after involvement of the inguinal lymph nodes, although it is probable that the disease had existed in the rectum in a very mild form since the initial symptoms. Likewise, ulcerative proctitis may exist for years before a stricture develops. In one patient under our observation the ulceration in the rectum was known to exist for five years before a stricture formed.

We wish to emphasize the occurrence and severity of the systemic reaction which is seen only occasionally in men but in the greater majority of Negro women. In such instances the disease is devastating, causing invalidism for years and acting occasionally as a secondary cause of death. In our series scarcely half the Negro women sustained a systemic reaction according to our records, but we are inclined to believe that the majority of them do have a systemic reaction since the patients who gave no history of such a reaction were patients who had had the disease for many years, but, being of an unobserving class, had no doubt forgotten or misinterpreted the symptoms. In many cases in Negro women the first symptom complained of is diffuse abdominal cramps. A temperature as high as 39 C. (102.2 F.) is not uncommon. Anorexia is prominent and persistent and is accompanied by a sharp loss of weight. Nausea and vomiting are uncommon but may occur. Extreme malaise and weakness may be present. Diffuse pains in the joints with occasional swelling and apparent deformity may be encountered and are one of the features which make a hopeless invalid of the patient. Any of these symptoms may remain for years unless relieved by treatment with antimony and potassium tartrate.

The appearance of the lesion in the rectum is fairly characteristic. In the early stages, when ulcerative proctitis is present without narrowing of the lumen, the mucosa is edematous, thickened and studded here

and there with tiny ulcers which appear superficial. This proctitis is limited almost invariably to an area from 1 to 6 inches (2.5 to 15 cm.) above the anal margin. Above this area the mucosa is normal. A moderate amount of blood and pus may be seen in the lumen, and their presence in the stool may be one of the first symptoms noted by the patient.

The formation of a stricture, which in our experience occurs in a far greater percentage of cases in the Negro than in the white race, occurs at the site of the proctitis justed noted. Digital examination of the rectum in over two hundred Negro women with benign stricture of the rectum, during the last fifteen years, disclosed that in nearly every case the upper limits of the growth can be reached with the examining finger if the lumen of the stricture permits the finger to pass. The mucosa in the upper portion of the rectum and sigmoid flexure is invariably normal. The mucosa just above the point of the stricture may show varying degrees of thickening and infiltration which increases or diminishes according to the constriction of the stricture. The sense of firmness and smooth nodular infiltration is so characteristic in a Negro that carcinoma scarcely need be considered in the differential diagnosis.

In a vast majority of patients the site of the stricture is within 5 cm. of the mucocutaneous line. The involvement does not extend into the anus proper, but a secondary infiltration of the surrounding skin tabs is present. This is presumably due to secondary stasis and chronic inflammation resulting from the persistent discharge from the rectum. We have seen rather large and painful masses about the anal margin disappear under treatment with antimony and potassium tartrate. The mucosa of the rectum external to the stricture is invariably infiltrated and ulcerated.

Single or multiple fistulas may develop in an early stage of the disease. The internal opening is above the stricture and when the constriction becomes complete conducts the fecal current out through the single or many discharging sinuses located about the rectum.

DIFFERENTIAL DIAGNOSIS

The disease, if stricture of the rectum is admitted to be part of the picture, is characteristic and should not be confused with any other disease except perhaps chancroidal bubo and tuberculosis of the inguinal lymph nodes. Culture of the pus obtained from the groin reveals no growth. It appears, however, that tuberculosis of the inguinal lymph nodes is rare, and many cases of lymphogranuloma inguinale have erroneously been diagnosed as such in the past. Injection of tuberculous pus into a guinea-pig will, of course, produce tuberculous lesions. Microscopically the lymph nodes resemble tuberculosis in that there is

evidence of chronic inflammation in each with accompanying giant cells. If a lymph node is excised in the acute stage, section should show tiny yellowish abscesses which on microscopic examination with the ordinary stains is seen as a necrotic mass resembling caseation which is surrounded by a palisade of epithelioid cells (fig. 2). This area of necrosis may be round but frequently is star-shaped. When present to a marked degree this palisading of epithelioid cells is so characteristic that the diagnosis is practically certain. In tuberculosis one occasionally sees the epithelioid cells around a tubercle arrange themselves in this fashion,

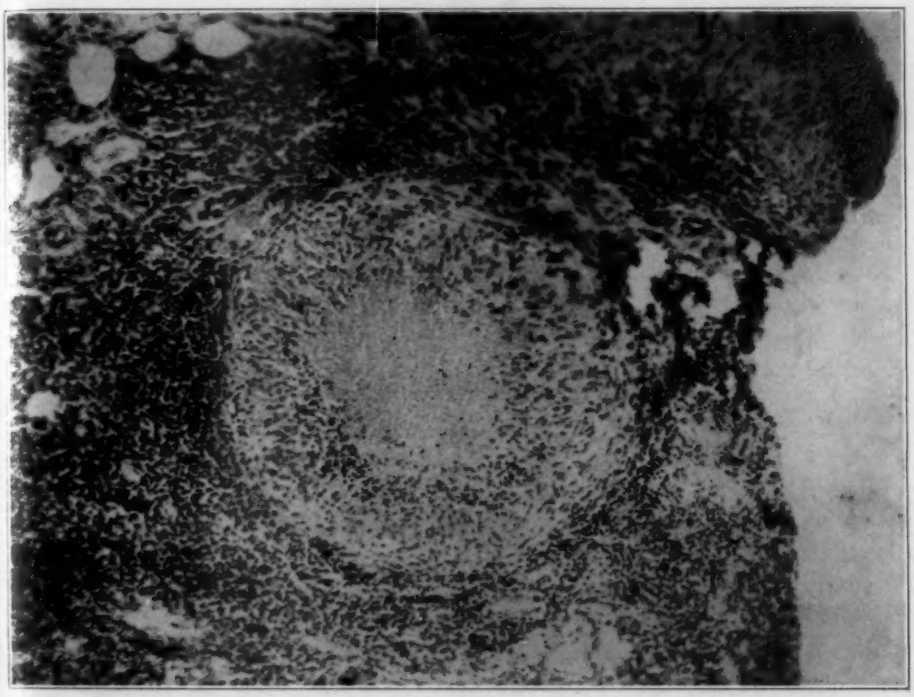

Fig. 2.—A low power photomicrograph of a tiny abscess of a suppurating lymph node from the patient shown in figure 1. Note the caseous center with the palisade of epithelioid cells at the periphery. These abscesses may be star-shaped instead of round and are characteristic of the disease, provided the lymph node is removed before the suppurative process has healed.

but never have we seen such a typical arrangement as is found in lymphogranuloma inguinale. Unfortunately the node must be in the proper stage of suppuration or the lesion will be indistinguishable from tuberculosis. In this case the Frei test should, however, clarify the diagnosis. Except on rare occasions a chancroidal bubo is accompanied or immediately preceded by an extensive ulceration about the genitals, which is never present in lymphogranuloma as a primary

lesion. The disease should not be confused with granuloma inguinale, which does not affect the lymph nodes but manifests itself as a granulomatous ulceration of the genital region which on certain occasions may be present in the groin. Antimony and potassium tartrate is a specific in the treatment of granuloma inguinale but is only moderately beneficial as a therapeutic agent in the treatment of lymphogranuloma inguinale. Lymphogranuloma should not be confused with syphilis, since the lymph nodes in the latter disease have no evident inflammation about them and never suppurate unless complicated by a secondary disease. Moreover, in our experience, inguinal adenitis secondary to a syphilitic ulcer about the anus or perineum usually is unilateral and should, of course, respond to treatment with arsphenamine. We wish to repeat that with a satisfactory antigen the Frei test is extremely reliable and in our hands has been very helpful. Obviously, if the antigen is obtained from a patient who previously had chancroidal disease, a false positive reaction might be obtained. Moreover, in a patient who has had lymphogranuloma years previously, a positive reaction will develop when the active lesion is in reality caused by an entirely different disease. Such pitfalls must be kept in mind, because in a large series such sources of error will be encountered.

TREATMENT

When the disease is confined to inguinal adenitis the treatment need not vary much from the treatment of any subacute or chronic inflammation. When pus accumulates it may be evacuated by incision or aspiration. In one of our cases aspiration resulted in a local cure. If sinus formation and enlarged glands in the groin persist for weeks and months the inguinal lymph chain may be excised with a resulting cure of the local process, which may shorten the period during which dressings are needed.

Antimony and potassium tartrate, from 5 to 7 cc. of a 1 per cent solution twice a week for from twelve to fifteen doses, as recommended by many, has been mildly successful in our hands. Two of the patients to whom we gave this were relieved of severe abdominal pain and cramps, which were a part of their systemic reaction to the disease. A large granulomatous and papillomatous mass about the anus of another patient decreased sharply with this treatment. As would be expected the antimony and potassium tartrate did not exert any influence on the rectal stricture. We wish to issue a warning, however, relative to the toxicity of the drug. On several occasions the injection of 5 cc. of a 1 per cent solution produced tachycardia, weak pulse, nausea and vomiting which definitely were not of psychic origin. In another instance after one of the patients had had ten doses of 5 cc. of a 1 per cent solution at semiweekly intervals she awoke one morning with

severe weakness of practically all the muscles in one lower extremity. When seen several days later the weakness was still present but not so prominent. The patient later regained her normal muscle power.

ANALYSIS OF CASES

Reference to tables 1, 2 and 3 will obviate the necessity of a detailed discussion of our cases. As can be seen in table 1, only 28.5 per cent of the patients with stricture of the rectum and 33.3 per cent of the patients without stricture of the rectum had a positive Wassermann or

TABLE 1.—*Relation of Lymphogranuloma Inguinale to Syphilis on the Basis of Positive or Negative Wassermann or Kahn Tests*

	Number of Patients	Wassermann or Kahn Test			
		Positive		Negative	
		Number	Per Cent	Number	Per Cent
With stricture	14*	4	28.5	10	71.5
Without stricture (inguinal adenitis, proctitis)	9	3	33.3	6	66.6

* These patients were Negro women.

TABLE 2.—*Clinical Manifestations of Lymphogranuloma Inguinale in Twenty-Three Patients*

	Men	Women
White	1	2
Negro	3	17
Adenitis	4	5 (3 supp.)
Ulcerative proctitis	1	5
Stricture	0	14
Anal lesions	1	3
Rectal fistulas	0	2
Systemic reaction	0	7*

* Systemic reaction was evidenced by malaise, anemia, loss of weight, vertigo, abdominal pain, nausea, fever, vomiting and arthritis.

Kahn reaction. Antisyphilitic treatment was given to a number of the patients with rectal stricture (some of whom had a positive Kahn reaction), and in no instance did we observe any favorable results from the therapy. In the group of patients with a positive Kahn reaction are included one or two patients whose reaction was negative when they were seen by us but who had a definite history of syphilis followed by a course of treatment. This percentage of 28 and 33 is no greater than that which might be expected in any group of patients of the same social status. The frequency of occurrence of the various symptoms and signs are given in table 2 and are discussed in the section on clinical manifestations.

TABLE 3.—*Protocol of Cases*

Patient	Age	Sex	Race	Wassermann or Kahn Test	Frei Test	Inguinal Lymphadenitis	Rectal Involvement		Additional Data
							Ulceration	Stricture	
1. M. B.	25	F	N	— (1+)	++++	No	Blood and pus in stool for a year; ulcerated and edematous mucosa; multiple large external tabs	No, but slight narrowing	Arthritis; loss of weight and strength for 6 months; marked improvement with antimony and potassium tartrate
2. P. W.	27	F	N	—	+++	No	Blood and pus in stool for 2 years; pain; edematous and ulcerated mucosa; large external tabs	No	Improvement with antimony and potassium tartrate; abdominal pain relieved
3. L. B.	28	F	N	—	.....	No	For 3 weeks	No	Abdominal pain most significant symptom
4. F. H.	61	M	W	—	++++	Began on left side 8 weeks before; suppuration 6 weeks before	No	No	Guinea-pig inoculated with pus from groin gave negative reaction for tuberculosis
5. B. M.	20	M	N	—	+++	Swelling in each groin began 1 year before; suppuration 2 weeks later; healed in 3 weeks	Ulcerated mass 2 by 3 cm. on anal margin developed 9 months before; slight edema and ulceration of mucosa	No, but slight narrowing	
6. L. J.	20	M	N	—	+++	Swelling in left groin began 6 months before; nodes above and below inguinal ligament with more below	No	No	Sinus of unexplained etiology in midportion of thigh
7. I. W.	26	F	W	—	++++	No; a few enlarged nodes not noticed by patient	Operation for fistula 5 years before; blood and pus in stool since then	Yes, of at least 2 years' duration	Fever, arthritis and malaise for preceding 3 months; no antisyphilitic treatment
8. E. H.	37	F	N	—	2/1/34 ++ 3/4/34 ++++	No	Blood and pus first noticed in stool 7 years before; edema and ulceration of mucosa for next 4 years	Yes, of 3 years' duration; barium sulphate enema revealed narrowing as high as sigmoid flexure	No antisyphilitic treatment; no stricture when first seen, in 1931
9. B. S.	58	F	N	—	+++	No	Healed, but stricture present	History suggests 25 years' duration	No antisyphilitic treatment
10. M. G.	34	F	N	—	++	No	Blood and pus in stool 7 years before; ulcerated and edematous mucosa	Of 5 years' duration	No antisyphilitic treatment; stricture just beginning when first seen 7 years before (1927)

11. M. W.	31	F	N	—	+++	No	Healed, but stricture present	When first seen 7 years before	No antisyphilitic treatment; no improvement in stricture with antimony and potassium tartrate
12. H. B.	39	F	N	—	++++	No	History inadequate, but had symptoms for 13 years	When first seen 11 years before	Wassermann test negative in 1923; antisyphilitic (?) treatment in 1929; Kahn test negative in 1934
13. L. F.	31	F	N	—	++++	No	No history	For at least 2 years	No antisyphilitic treatment
14. B. M.	23	F	N	—	+++	Suppurating node in right groin 4 years before; large node still present	Pain, blood and pus from rectum began 3 years before	For at least 6 months	Systemic symptoms—vertigo, nausea, pain in hips, thighs and abdomen persisted
15. A. J.	32	F	N	—	++ to +++	Suppurating nodes in right groin 11 years before	Blood and pus from rectum and multiple fistulas of 5 years' duration	For at least 3 years	No systemic symptoms
16. C. Q.	34	F	N	—	++++	No	Pus in stool, and mild pain for past 3 years	For at least 2 years	Loss of weight, anorexia and anemia
17. A. F.	47	F	N	++++	+++	No	Healed, but stricture present	History suggests 8 years' duration	
18. M. O.	42	F	N	4+ 7 years ago, but neg. now	++++	No	Blood and pus first noted in stool 12 years before	For at least 7 years	Wassermann test became negative after antisyphilitic treatment 7 years before
19. M. B.	33	F	N	++++	+++	No	Blood and pus in stool 7 years before following hemorrhoidectomy	Duration unknown	
20. E. S.	39	F	N	++++	++++	No	Itching and condylomatous mass about anus noted 1 year before	Yes, but admits finger	Receiving antisyphilitic treatment
21. N. W.	23	F	N	++++	++++	No	Edematous and ulcerated mucosa extended into sigmoid flexure; 6 months' duration	No	Sudden onset of nausea, vomiting and abdominal cramps preceded blood and pus in the stool; still present after 6 months
22. L. G.	37	M	N	++++	++++	Swelling in right groin began 5 months before; suppuration 1 month before	No	No	
23. M. B.	26	F	W	++++	++++	Swelling began in each groin 10 days after rectal symptoms; right side suppurated 8 weeks before	Blood and pus in stool 6 months before; ulcerated and edematous mucosa	No	History of perverted sexual relations

SUMMARY

During the past year we have observed twenty-three cases in which we were convinced that the condition could correctly be classified as lymphogranuloma inguinale. The Frei test was positive in the entire group in which there appeared all three of the major manifestations of the disease, namely, inguinal adenitis, ulcerative proctitis and rectal stricture. On one occasion, however, the reaction to the Frei test was doubtfully positive, but a repetition of the test revealed a strongly positive reaction. The test was made on numerous patients with other diseases, such as syphilis, tuberculosis of the inguinal lymph nodes, stricture of the rectum accompanying obviously idiopathic ulcerative colitis (one case) and other diseases, but was negative in all instances. The disease is mild in men, consisting chiefly of suppurative inguinal adenitis which leaves no residual disease or disability after it heals. The most serious manifestations are encountered in Negro women, in which group systemic reactions are most common and rectal strictures occur. We are of the opinion that the greater portion of the benign rectal strictures so commonly observed in Negro women are due to lymphogranuloma. We observed one patient who had ulcerative proctitis of the type included in our group of cases in whom there developed a stricture of the rectum which was the same type as the strictures reported in this series. The fact that the Frei test was positive in these cases lent support to the probability that lymphogranuloma was the etiologic factor. The incidence of a positive Kahn test of 28.5 per cent in our series of patients with stricture of the rectum appears too small to suggest the possibility of syphilis being the cause. Antimony and potassium tartrate, although not a specific, causes improvement in the acute cases but does not appear to influence favorably the rectal strictures.

NOTE.—Since this article was prepared for publication eighteen additional cases have been observed. The incidence of a positive Wassermann or Kahn reaction in the combined series of patients with stricture of the rectum is not changed appreciably.

COMBINED AND SEPARATE EFFECTS OF BILE, PANCREATIC SECRETION AND TRAUMA IN EXPERIMENTAL PEPTIC ULCER

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Nonhealing peptic ulcers simulating those occurring in man were rarely obtained by any experimental method until Mann [1] in 1923 demonstrated that they could be produced at will in dogs subjected to "duodenal drainage." Later Morton,[2] McCann,[3] Dragstedt,[4] Matthews and Dragstedt,[5] and Weiss and Gurriaran [6] produced similar ulcers in 100 per cent of dogs operated on in the same manner. The peptic ulcers so obtained occurred in the total absence of alkaline pancreatic juice, bile and duodenal secretions, which had been deviated into the lower intestinal tract. While the aforementioned authors conceded that the action of unneutralized acid is an important factor in the production of ulcers, McCann believed that his experiments showed that trauma was an equally, if not more important, factor in the causation of the ulcers obtained by him. The present investigation was undertaken in an attempt to determine the relative effects of unneutralized acid gastric chyme and trauma in the production of experimental peptic ulcer in dogs.

Early investigators studied the effect of acid on gastric mucous membrane of dogs by administering relatively large doses of dilute hydro-

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From the Department of Surgery, School of Medicine, Tulane University of Louisiana.

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2. Morton, C. B.: Observations on Peptic Ulcer, Ann. Surg. **85**:207 and 879, 1927; **87**:401, 1928.

3. McCann, J. C.: Control of Acidity, Am. J. Physiol. **89**:483, 1929; Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

4. Dragstedt, L. R.: Contributions to the Physiology of the Stomach: XXXVIII. Gastric Juice in Duodenal and Gastric Ulcers, J. A. M. A. **68**:330 (Feb. 3) 1917.

5. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265, 1932.

6. Weiss, A. G., and Gurriaran, G.: Ulcères chroniques gastro-duodénaux expérimentaux créés par la dérivation des sucs alcalins duodénaux, Bull. et mém. Soc. nat. de chir. **36**:6, 1930.

chloric acid. Erosions and hemorrhagic spots were inconsistently obtained in inverse proportion to the amount of food allowed during the experimental period. This method has recently been revived and has again proved unsatisfactory. However, if gastric acidity is altered by unphysiologic operative methods, chronic ulcers not infrequently occur.

Friedman [7] found that ulcers in the pyloric region produced by submucous injection of silver nitrate became chronic when associated with hyperacidity resulting from pyloric stenosis. O'Shaughnessy,[8] after transplanting patches of jejunal mucosa into the wall of the stomach, performed a gastro-enterostomy "en Y" with occlusion of the pylorus. Following this procedure ulcers occurred in the transplants. Dott and Lim [9] reported that in most instances marginal ulcers formed after the establishment of an experimental gastro-enterostomy whenever the pylorus was occluded. This finding was in agreement with the clinical experience of von Haberer,[10] who observed that jejunal ulcers developed in 12 of 71 patients in whom he performed combined gastro-enterostomy and pyloric occlusion, whereas ulcers developed in only 3 of 275 patients without occlusion. That pyloric occlusion favors a high gastric acidity has been shown experimentally. Friedman and Hamburger [11] found an increase in gastric acidity after narrowing the pylorus with a purse-string suture; defects which they produced in the gastric mucosa failed to heal and frequently developed into peptic ulcers. Bolton [12] also showed that experimentally produced ulcers healed more slowly if the pylorus was constricted by rubber bands. Similar delay in healing was reported by Ivy.[13] That experimentally produced gastric ulcers healed more rapidly when the pylorus was splinted was shown

7. Friedman, G. A.: The Influence of Removal of the Adrenals and One-Sided Thyroidectomy upon the Gastric and Duodenal Mucosa: The Experimental Production of Lesions, Erosions, and Acute Ulcer, J. M. Research **32**:287, 1913.

8. O'Shaughnessy, L.: Etiology of Peptic Ulcer, Lancet **1**:177, 1931.

9. Dott, D. M., and Lim, R. K. S.: Experimental Jejunal Ulcer, Quart. J. Exper. Physiol., supp. 11, 1923, p. 109.

10. von Haberer, H.: Gastric, Duodenal and Peptic Ulcer, Deutsche Ztschr. f. Chir. **172**:1, 1922.

11. Friedman, J. C., and Hamburger, W. W.: Experimental Chronic Gastric Ulcer, J. A. M. A. **63**:380 (Aug. 1) 1914.

12. Bolton, Charles: Ulcer of the Stomach, London, Edward Arnold & Co., 1913; Further Observation on the Pathology of Gastric Ulcer, Proc. Roy. Soc., London, s. B **82**:233, 1910.

13. Ivy, A. C.: Studies on the Experimental Gastric and Duodenal Ulcer, Am. J. Physiol. **49**:143, 1919-1920; Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Jan.) 1920; Studies on Gastric and Duodenal Ulcer, J. A. M. A. **75**:1540 (Dec. 4) 1920; Secretion Pars Pylorica, Am. J. Physiol. **57**:51, 1921.

by Hughson;[14] and Elman and Rowlette[15] demonstrated that division of the pyloric sphincter permitted rapid neutralization of gastric acid.

Bickel,[16] in 1909, obtained a perforating jejunal ulcer by closing the pylorus, performing a gastro-enterostomy and creating external biliary and pancreatic fistulas. He promptly recognized that the presence of bile and pancreatic juice in the upper part of the jejunum might be one of the important factors in preventing the formation of jejunal ulcers after gastro-enterostomy. In 1914 Langenskiöld[17] performed the same operation which Mann later termed the "duodenal drainage operation." He severed the duodenum a short distance from the stomach and closed the distal end, sectioned the jejunum several centimeters below the junction of the duodenum with the jejunum, and joined the aboral end to the stump of the duodenum. The oral end of the jejunum he anastomosed to a loop of jejunum further caudad, thus shunting the duodenal, pancreatic and biliary secretions into the midportion of the small intestine. A month later an ulcer was found in the short segment of duodenum joining the stomach and jejunum. Prior to this, in 1898, Chlumsky[18] reported similar experiments in which he deviated all the duodenal secretions into the fundus of a gastro-enterostomized stomach, as was later done by McCann. Keppich,[19] in 1921, repeated Chlumsky's experiment, and in 2 dogs in which 6 cm. of the pars pylorica was left in connection with duodenum jejunal ulcers formed near the anastomosis. In 2 other animals the operation was modified to the extent that much of the distal end of the stomach was resected. In neither of these dogs did an ulcer occur. In 2 other animals he combined Chlumsky's and Langenskiöld's operations so as to deviate the duodenal juices into the fundus of a stomach which emptied through the pylorus into a short segment of duodenum and then into the jejunum; an ulcer did not form. From this work Keppich concluded that a mixture of pyloric and duodenal secretions is more likely to permit

14. Hughson, W.: Relation of Pylorus to Duration of Experimental Gastric Ulcer, Arch. Surg. **15**:66 (July) 1927.

15. Elman, R., and Rowlette, A. P.: The Rôle of the Pyloric Sphincter in the Behavior of Gastric Acidity, Arch. Surg. **22**:426 (March) 1931.

16. Bickel, A.: Beobachtungen an Hunden mit exstirpiertem Duodenum, Berl. klin. Wchnschr. **46**:1201, 1909.

17. Langenskiöld, F.: Ueber die Widerstandsfähigkeit einiger lebender Gewebe gegen die Einwirkung eiweisspaltender Enzyme, Skandinav. Arch. f. Physiol. **31**:1 1914.

18. Chlumsky, V.: Ueber die Gastroenterostomie, Beitr. z. klin. Chir. **20**:231 and 487, 1898.

19. Keppich, J.: Ueber das Ulcus pepticum Jejuni nach Pylorusausschaltung, Zentralbl. f. Chir. **48**:118, 1921; Künstliche Erzeugung von chronischen Magengeschwüren mittels Eingriffen am Magenvagus, Wien. klin. Wchnschr. **34**:118, 1921.

the formation of a jejunal ulcer than the duodenal secretions alone. Koennecke,[20] in 1922, tested this theory by isolating the pars pylorica and the first portion of the duodenum (apparently above the openings of the pancreatic and biliary ducts), closing both ends and draining this segment into a loop of ileum. The main portion of the stomach was then drained into the second portion of the duodenum as in the Billroth operation I; ulcers did not form. When, in addition to this operation, he cut the splanchnic nerves on both sides, chronic duodenal ulcers developed in all 4 animals.

In 1910, Moutier[21] made a total gastric pouch, and in 3 of the animals a perforating gastric ulcer occurred. He made the further interesting observation that in these stomachs through which food did not pass the ulcers did not show the usual predilection for the lesser curvature. Similarly, Matthews and Dragstedt[5] obtained ulcers in a totally isolated stomach, as well as in a large Pavlov pouch accessory stomach, in both of which the motility of digestion was absent. They called attention to the fact that the remainder of the stomach from which the pouch was made did not ulcerate.

Kapsinow[22] was the first to deviate bile from the gastro-intestinal tract. He implanted the fundus of the gallbladder into the pelvis of the right kidney and subsequently ligated the common duct. His animals rapidly lost weight, passed tarry stools, and died after two or more weeks. At autopsy 17 of 40 animals had acquired single or multiple ulcers varying in size from 2.5 to 5 cm. in diameter with punched-out, overhanging edges. He stated that Whipple produced ulcers by making a biliary fistula and later ligating the common duct, but criticized the work because of the possibility that infection, ascending through the fistulous tract to the duodenum or the liver, and not biliary drainage, caused the ulcers. As Kapsinow's dogs were in poor condition before death, it is possible that inanition played some part in the production of the ulcers in his series. Mueller,[23] Köllicher,[24] Bidder,[24] Schmidt,[24] Beatti[24] and others produced ulcers "after exclusion of the liver." Boll-

20. Koennecke, W.: Experimentelle Untersuchungen über die Bedeutung des Pylorusmagens für die Ulcusgenese, Arch. f. klin. Chir. **120**:537, 1922; Zentralbl. f. Chir. **50**:276, 1923; Ulcusgenese und Gastroenterostomie, ibid. **53**:1866, 1926.

21. Moutier, F.: De l'ulcère chronique spontané chez le chien à estomac isolé, Arch. d. mal. de l'app. digestif **4**:49, 1910.

22. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestine, Ann. Surg. **83**:614, 1926.

23. Mueller, Ludwig: Das corrosive Geschwür im Magen und Darmkanal (Ulcus ventriculi perforans chronicum rotundum), und dessen Behandlung, Stuttgart, Ferdinand Enke, 1860, p. 274.

24. Quoted by Greggio: Des ulcères gastro-duodénaux, Arch. de méd. expér. et d'anat. path. **27**:533, 1916-1917.

man and Mann [25] reported that perforating ulcers occurred when dogs were fed coarse food following partial hepatectomy, creation of a true Eck fistula and ligation of the common duct, procedures which probably influenced the quantity of bile entering the duodenum. In a second series of experiments they obtained similar results with usual diets after ligation of the common duct and removal of the gallbladder, and, in a few instances, after partial removal of the liver. Berg and Jobling,[26] by excluding bile, obtained ulcers in 4 of 7 dogs in which a biliary fistula was made, in 6 of 11 dogs in which a fistula was first made and then obstructed, and in 3 of 5 dogs in which the common duct was ligated. Ivy and Fauley [27] obtained duodenal ulcers in 2 of 20 dogs in which the common duct was obstructed; Morton also obtained ulcers after obstructing the common duct, and Ivy [13] noted ulcers in 6 of 10 dogs with permanent biliary fistulas.

Rous and McMaster,[28] using Berg and Jobling's [26] method of producing biliary drainage, were unable to obtain peptic ulcers. Elman,[29] using the same technic, observed no ulcers in many dogs, some of which were kept alive for as long as four months. Puestow,[30] in a study of biliary secretion following exteriorization of the duodenal segment containing the ampulla of Vater, made no mention of having observed ulcers. That ulcers did not develop in the animals of all of the latter investigators, who were able to keep their dogs in good condition for a period of months, suggests that some factor other than the absence of bile is responsible for the production of ulcers in the dogs with inanition. Since Ivy [13] has shown that ulcers are more likely to occur in experimental animals in poor condition, or with pneumonia, it seems probable that some of these dogs might have acquired ulcers because of their malnutrition and did not have malnutrition because of their ulcers. Certainly the dogs with obstruction of the biliary tract or with removal of part or all of it (hepatectomy) had sufficient metabolic

25. Bollman, J. L., and Mann, F. C.: Chronic Duodenal Ulcer in Animals with Eck Fistulas on Certain Diets, Arch. Path. **4**:492 (Sept.) 1927; Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

26. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcers, Arch. Surg. **20**:997 (June) 1930.

27. Ivy, A. C., and Fauley, G. B.: Chronicity of Ulcer in the Stomach and Upper Intestine, Am. J. Surg. **11**:531, 1931.

28. Rous, P., and McMaster, P. D.: Method for the Permanent Sterile Drainage of Intra-Abdominal Ducts as Applied to the Common Duct, J. Exper. Med. **37**:11, 1923.

29. Elman, R.: Gastric Acidity in Pancreatic Drainage, Arch. Surg. **16**:1256 (June) 1928; Spontaneous Peptic Ulcers of the Duodenum Following the Total Loss of Pancreatic Juice, ibid. **23**:1030 (Dec.) 1931.

30. Puestow, C. B.: The Activity of Isolated Intestinal Segments, Arch. Surg. **24**:565 (April) 1932.

disturbances to acquire ulcers as a result of more than one factor. An experiment herein reported definitely indicates that the deviation of bile alone from the duodenum does not result in the formation of peptic ulcer.

Deviation of pancreatic secretion alone into the lower intestinal tract has not been reported. However, by exclusion or total loss of the pancreatic juice, Elman and Hartmann [31] obtained duodenal ulcers in 6 dogs in which they accomplished pancreatic drainage. They were able to keep their animals alive for at least thirteen days by means of intraperitoneal injections of lactate Ringer's solution (as devised by Dr. Hartmann) in 5 per cent dextrose. Jona,[32] after tying the pancreatic duct in 11 animals, found ulcers in the duodenum, the stomach and the jejunum, and Gallagher [33] observed delayed healing of traumatic ulcers after ligation of the duct. In view of the alkalinity and large quantity of the pancreatic secretion it seems reasonable that the absence of its neutralizing effect might have delayed healing in the latter's animals, but experiments herein included do not substantiate the work of Elman and Hartmann.[31] It seems that the ulcers obtained by Jona [32] could have been due to other factors than the absence of the neutralizing effect of pancreatic juice.

The combined elimination of bile and pancreatic juice was first done by Kehrer.[34] He implanted the pancreatic duct in the appendix and anastomosed the gallbladder to the same viscus after ligating the common duct. In 6 dogs that died he found lesions which were macroscopically and microscopically typical peptic ulcers. Grey [35] likewise obtained ulcers in 2 dogs after transplanting the bile and pancreatic ducts into the terminal ileum. Mann and Williamson [36] transplanted both the bile and the pancreatic ducts into the lower part of the ileum and obtained single and multiple indurated ulcers in the region between

31. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of the Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

32. Jona, J. L.: A Further Contribution to the Experimental Study of Duodenal Ulcer, M. J. Australia **1**:316, 1919; Experimental Study of Duodenal Ulcer, Physiol. Abstr. **4**:412, 1919.

33. Gallagher, W. J.: Acute Traumatic Ulcers of the Small Intestine: Observations on the Effects of the Application of Clamps on the Gastro-Intestinal Tract; an Experimental Study, Arch. Surg. **15**:689 (Nov.) 1927; Acid on Jejunal Transplants, ibid. **17**:279 (Aug.) 1928; Acid on Peptic Ulcer, ibid. **17**:613 (Oct.) 1928.

34. Kehrer, J. K. W.: Ueber die Ursache des runden Magengeschwüres, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:679, 1914.

35. Grey, E. G.: Duodenectomy: Its Effect upon the Life of an Animal, Surg., Gynec. & Obst. **28**:36, 1919.

36. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1922.

the pylorus and the ampulla of Vater in 10 of 31 dogs. Ulcers occurred in 8 of 10 dogs in which they removed the entire duodenum, anastomosed the proximal end of the jejunum to the pylorus, and transplanted the bile and pancreatic ducts into the terminal ileum.

Mann and Williamson [36] reinitiated the study of ulcer formation following the deviation of all the alkaline duodenal contents into the lower intestinal tract. In 14 of 16 dogs subjected to "duodenal drainage," subacute or chronic ulcers similar to those found in man occurred in the third or fourth week on the posterolateral surface of the jejunum, just distal to the jejunopyloric anastomosis, whereas ulcers developed in only 2 of 10 dogs in which they resected the duodenum and transplanted the bile and pancreatic ducts into the jejunum near the point where the latter was anastomosed to the pylorus. According to McCann,[3] "In duodenal drainage Mann conceived of the gastric chyme as being ejected through the pylorus by gastric contractions, as if through a nozzle and impinging forcibly against the wall of a segment containing little, if any, alkali, the mechanical and chemical action of this stream leading to necrosis of the epithelium and the formation of ulcer."

By several experimental methods Morton [2] further confirmed the probability that the chronicity of ulcers and their failure to heal were due to the action of unneutralized acid gastric chyme and trauma. He excised pieces of mucosa from the lesser and greater curvatures of the stomach in 36 dogs and instituted "duodenal drainage." In from 50 to 62 per cent of these the defects in the antrum and on the lesser curvature were still present at subsequent observations. Similar defects in control animals healed within two weeks. Morton [2] believed that the defects on the lesser curvature persisted longer because they were subject to more trauma than those on the greater curvature. In 13 animals he transplanted jejunal "patches" with intact circulation into the gastric wall, and in addition performed "duodenal drainage." In 4 of these dogs ulcers developed in the "patches" on the lesser curvature, whereas no ulcers occurred on the greater curvature. Jejunal transplants in control dogs showed no marginal ulceration after fifteen days.

In the duodenum Mann and Williamson [36] believed that the mechanical factor contributing to the cause of ulcer was the force of the impinging stream of gastric chyme through the pylorus. In the stomach Morton [2] believed that the mechanical factors which localized the ulcers obtained by him were "the paucity of protecting rugae in the prepyloric segment, particularly along the 'Magenstrasse' with its poor blood supply and the convergence of the lines of force along the lesser curvature as suggested by Aschoff."

McCann [3] modified the original "duodenal drainage" operation to shunt the alkaline duodenal secretions from the distal side of the pylorus to the gastric side. His assumption was that the deviation of duodenal

contents into the fundus of the stomach might control gastric acidity. A test meal of meat and water given to 2 dogs preoperatively and postoperatively revealed, by fractional analysis, the same normal curves for free hydrochloric acid, total acid and combined chlorides before and after "modified duodenal drainage." Fractional gastric analyses before and after the performance of the original "duodenal drainage" operation revealed similar curves. On the basis of these findings, McCann [3] concluded that the mechanism for control of gastric acidity is intragastric, and that the level of gastric acidity is wholly independent of reflux of duodenal contents. This phase of McCann's work is open to criticism because only 2 animals were used, and the meat test meal which was given usually combines readily with hydrochloric acid to mask the actual acidity developed. Contradictory findings have been reported by Steinberg, Brougher and Vidgoff,[37] who, by the use of a test meal of 300 cc. of water containing extract of beef, observed a much higher acidity following "duodenal drainage" into the terminal ileum than was obtained in the normal stomach. These workers contended that the difference in acidity was not due to hypersecretion on the part of the stomach, since the acidity of a Pavlov pouch in the same animal remained unaltered.

McCann [3] obtained single or multiple subacute and chronic ulcers in the upper jejunum in 21 of 26 dogs on which he had performed his "modified duodenal drainage operation." The incidence and type of ulcers were the same as those obtained by Mann, but he emphasized trauma as a factor in the production of these ulcers more than the action of unneutralized acid gastric chyme. In one specimen hairs were embedded in the wall of the ulcer, and in another an ulcer that had perforated was plugged by a pyramidal piece of turnip. These, he believed, were implanted in the ulcer by the forceful impinging of the gastric contents onto the jejunum and the friction of coarse cellulose foods. He was particularly impressed with the forceful ejection of gastric chyme, because he observed roentgenologically that the whole prepyloric segment was thrown into a vigorous tonic contraction when a test meal was given.

Because the ulcers in his experiments developed in the presence of an unneutralized normal gastric acidity, McCann concluded that the alkaline duodenal contents protect against ulcer formation "by some type of buffer or diluting action beyond the pylorus that terminates the acid peptic activity of the gastric chyme." That the gastric acidity might have been abnormally high, particularly when the original "duo-

37. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: Changes in the Chemistry of the Contents of the Stomach Following Gastric Operations, Arch. Surg. **15**:749 (Nov.) 1927.

denal drainage" was performed, has been commented on. That it was abnormally high after the modified operation is not improbable, for it is possible that gastric peristalsis forced gastric contents retrogradely into the duodenal loop or at least seriously interfered at times with the free and continuous flow of the duodenal contents into the stomach.

Steinberg and Proffitt [38] also believed that trauma plays a part in the production of the ulcers that occur in animals subjected to "surgical duodenal drainage." They found that ulcers occurred just distal to the anastomosis in 100 per cent of dogs when the jejunum was anastomosed end-to-end with the pylorus, whereas if the side of the jejunum was anastomosed to the end of a pylorectomized stomach, ulcers were obtained in only 43 per cent of the animals. They also observed that following the latter Billroth type of anastomosis ulcers occurred more frequently when they produced a kink just distal to the anastomosis. This, they believed, produced stasis and allowed the acid gastric chyme more time to exert its corrosive action.

The experiments of Matthews and Dragstedt [5] indicate that the action of acid gastric juice is more important than trauma in the production of peptic ulcer. They reproduced in dogs a counterpart of the Meckel's diverticulum of man by implanting a small isolated pouch of gastric wall into the jejunum and into the ileum. In the intestinal mucosa near the transplant, chronic ulcers occurred in 85 per cent of instances in the jejunum and in 100 per cent in the ileum. These ulcers occurred in the absence of unaccustomed trauma and could have been produced only by the corrosive action of acid gastric juice. These authors repeated the "duodenal drainage" experiment, but anastomosed the duodenum to the jejunum only 40 cm. below the anastomosis of the jejunum with the pylorus. Only 1 dog of 21 so operated on acquired a jejunal ulcer. In this experiment regurgitation of duodenal contents apparently prevented the formation of ulcers, and the trauma emphasized by McCann [3] was evidently not great enough to produce destruction of the jejunum. In another group of animals in which the pyloric musculature was completely excised and regurgitation prevented by placing a one-way valve above the point of drainage of the duodenal contents into the jejunum, ulcers developed in 100 per cent, showing that the corrosive action of unneutralized acid gastric juice alone will cause ulcer formation. When in normal dogs a valve was placed in the pylorus to prevent regurgitation of duodenal contents, both the free and the total acidity in the gastric contents were raised above normal when a standard test meal was given. Neutralization of 0.5 per cent hydrochloric acid placed in the stomach was delayed, as was the healing of

38. Steinberg, M. E., and Proffitt, J. C.: The Etiology of Postoperative Peptic Ulcers, Arch. Surg. **25**:819 (Nov.) 1932.

acute ulcers produced by the injection of silver nitrate into the gastric mucosa. Prevention of regurgitation of duodenal contents also resulted in the occurrence of ulcers in transplants of intestinal mucosa sutured into defects made in the gastric mucosa. Matthews and Dragstedt [5] believed that these experiments substantially support the contention that the chemical action of pepsin hydrochloric acid (of the concentration found in pure gastric juice) can by itself produce typical chronic peptic ulcer. They stated that it should be emphasized that no evidence has been offered which contradicts the possible deterrent action of gastric motility and the mechanical action of coarse food in the healing of acute lesions of the stomach or duodenum. They concluded, however, that of these three factors, the chemical action of the acid gastric secretion seems to be the most important both in the production of acute peptic ulcer and in its subsequent chronicity.

The following investigations were undertaken in order to evaluate the effect of trauma in the production of peptic ulcers and to determine the combined and relative values of bile and pancreatic juice in the prevention of ulcer.

I. EFFECTS PRODUCED BY DRAINAGE OF THE DUODENAL CONTENTS INTO THE PREPYLORIC SEGMENT OF THE STOMACH

This study on the etiology of peptic ulcer is based on the well known experimental evidence that ulcers develop just distal to the anastomosis of the jejunum and the pylorus in 100 per cent of dogs when "surgical duodenal drainage" is performed. To evaluate better the rôles played by trauma and unneutralized acid gastric contents, a modified duodenal drainage operation (fig. 1) was performed in order that duodenal reflux could be mimicked. The duodenal contents instead of being deviated into the fundus of the stomach, as was done by McCann,[3] were deviated into the prepyloric portion of the stomach just proximal to the anastomosis of the pylorus with the jejunum (fig. 1). By this means the alkaline secretions could mix with the acid gastric contents as they were ejected from the stomach and possibly neutralize these to such an extent that ulceration in the jejunum would not occur unless trauma, as is emphasized by McCann,[3] is an important factor in the production of ulcer.

METHOD

Moderately large healthy dogs that were already accustomed to kennel life were used in these experiments. The surgical procedure was performed under aseptic conditions. Rubber-covered spring steel clamps were used to facilitate the making of the anastomoses, but no crushing clamps were used on tissue that was to be included in the anastomotic sutures. Silk was used throughout as suture material.

The abdomen was opened by a high midline incision. The pylorus was delivered into the wound, and the vessels on the upper and lower borders were clamped, divided and tied with silk. The pylorus was divided, and the duodenal end was ligated, inverted by a purse-string suture and covered with a piece of the hepaticoduodenal ligament. Just distal to the ligament of Treitz the jejunum was delivered and divided. The proximal end of the distal segment was anastomosed to the pyloric end of the stomach to reestablish continuity of the gastro-intestinal tract with the duodenum excluded. The distal or jejunal end of the isolated duodenum was anastomosed (end-to-side) to the prepyloric portion of the anterior wall of the stomach within 3 cm. of the jejunopyloric anastomosis (fig. 1).

By means of this technic the alkaline duodenal contents were shifted from the distal side of the pylorus to the proximal side at a point very near the pyloro-jejunal anastomosis so that gastric contents might be mixed with duodenal contents just as the former passed out of the stomach. It was thought that the mixing of acid gastric chyme and alkaline duodenal contents obtained in this manner would

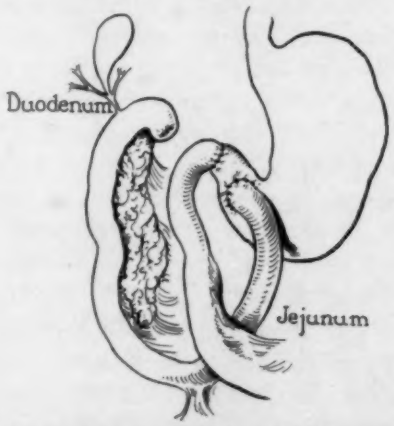

Fig. 1.—Drawing illustrating the "duodenal drainage operation" modified to mimic duodenal reflux by deviation of duodenal contents into the prepyloric portion of the stomach.

simulate to some extent that which is supposed to occur if reflux of duodenal contents actually does take place. The question was: Would the susceptible jejunal mucosa ulcerate in the presence of controlled gastric acidity, but under conditions permitting as much traumatization as occurs in the operations of Mann [1] and McCann? [2]

After operation the dogs were fed milk and syrup until they were able to take ordinary kennel rations, which consisted of coarsely ground up bones and foods of all sorts.

RESULTS

Eleven dogs lived from thirty to one hundred and eighteen days. In several of the dogs that died earlier no definite cause of death could be found, but these animals appeared to have an intoxication similar to that seen in animals with a high intestinal obstruction. As the prepyloric muscle is very thick and was usually found contracted at

necropsy, it seems not unlikely that this musculature exerted on the gastrojejunostomy a sphincteric action which caused a partial or intermittent obstruction of the duodenal segment. The 11 dogs that survived longer periods progressively lost weight and strength and died of inanition. In most instances the duodenal segment was sufficiently dilated and bile-stained to suggest that there had been a stasis of duodenal contents. In none of the dogs did a subacute or chronic ulcer develop in either the stomach or the jejunum.

COMMENT

The fact that peptic ulcers did not develop when the duodenal contents were deviated into the prepyloric portion of the stomach instead of into the fundic portion, as was done by McCann,[3] seems to indicate that the acid gastric chyme as it passed, or was ejected from, the pyloric end of the stomach into the jejunum, was sufficiently mixed with alkaline duodenal secretions to render it noninjurious to jejunal mucosa. That normal physiologic reflux of duodenal contents was duplicated is not claimed, for it is doubtful that the jejunum was bathed by alkaline duodenal contents more than a part of the time, but it is probable that the oncoming acid gastric contents were neutralized or diluted much in the same manner as they are by the reflux of alkaline duodenal contents. It is evident from these results that trauma is of little importance as a factor in the production of ulcer by "duodenal drainage."

That trauma plays an important rôle in the production of peptic ulcers following "surgical duodenal drainage," as believed by Mann,[36] McCann [3] and their associates, is not substantiated, as in this experiment "the force of the impinging stream ejected through the pylorus" was not altered, and ulcers did not form.

II. STUDY OF BILE AND PANCREATIC JUICE, RESPECTIVELY, IN THE PREVENTION OF EXPERIMENTAL PEPTIC ULCER

This study was undertaken to evaluate the rôles played by bile and pancreatic juice, respectively, in the prevention of peptic ulcer. By previous investigators these alkaline secretions had been simultaneously deviated, and each had been separately excluded by drainage to the outside, but each had not been separately deviated into the lower intestinal tract. Various authors, without basing conclusions on experimental evidence, had claimed greater neutralizing properties for one than for the other. These properties, the degree of alkalinity and the quantity of each secretion, had been accurately estimated, but their physiologic action in situ had not previously been determined.

In the present investigation, deviation of bile was obtained by ligating and dividing the common duct and anastomosing the fundus of the

gallbladder to the terminal portion of the jejunum (fig. 2). Deviation of the pancreatic juice was accomplished by transplantation of the main pancreatic duct into the terminal portion of the jejunum and ligation or avulsion of the accessory pancreatic duct (fig. 3).

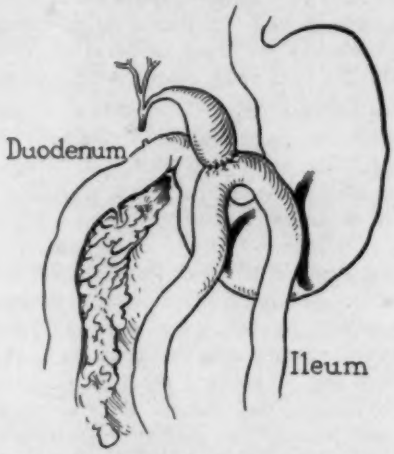

Fig. 2.—Drawing illustrating the deviation of bile into the terminal portion of the jejunum by an operation in which the common duct was divided and the gallbladder anastomosed to the jejunum.

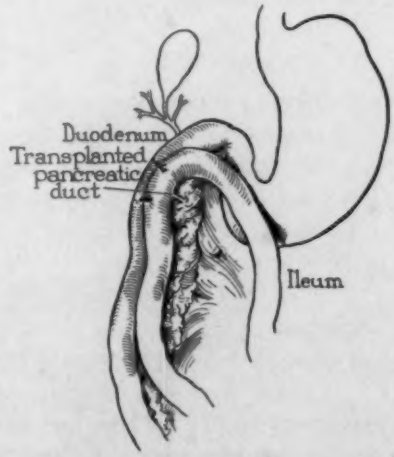

Fig. 3.—Drawing illustrating the deviation of pancreatic juice into the terminal portion of the jejunum by transplantation of the main pancreatic duct into the jejunum.

METHODS

Moderately small dogs were used in this study because in large animals the deep thorax was found to make the operative procedures extremely difficult.

Deviation of Bile (fig. 2).—The common bile duct was identified and sectioned between two ligatures placed just adjacent to the entrance of the duct into the

duodenum. The fundus of the gallbladder was delivered into the operative field with the aid of Allis clamps, which, after aspiration of the contents of the gallbladder, were replaced by "guy sutures" to facilitate making the anastomosis with the terminal portion of the jejunum. The stoma made in the two organs was usually less than 5 mm. in length. Some anastomoses were executed with a single row of silk mattress sutures, but in most of them a continuous silk Lembert suture was used in addition to a through and through continuous catgut hemostatic suture. In 3 of the dogs jejunojejunostomy was performed adjacent to the described anastomosis to short circuit intestinal contents away from the cholecystojejunostomy.

Deviation of Pancreatic Juice (fig. 3).—The small accessory pancreatic duct, which enters the duodenum 0.5 cm. below the papilla of Vater, was identified and either avulsed or ligated. The main pancreatic duct (about 3 mm. in diameter), which enters the duodenum about 4 cm. below the papilla of Vater, was identified and "reamed" out of the duodenum so that approximately 2 mm. of duodenal wall remained about its os. The resulting defect in the duodenum was closed with a single row of interrupted Lembert sutures, which did not invert enough tissue to produce a duodenal atresia. The distal portion of the jejunum was identified, and two silk sutures were passed through its medial wall into the lumen and out through a small stab wound placed in the opposite side of the gut. These sutures were then passed through the muscle and submucosa surrounding the os of the pancreatic duct and were brought back through the stab wound to cross the lumen and come out through the jejunal wall near their starting points. By means of these sutures the stump of the pancreatic duct was carefully introduced and drawn through the stab wound into the lumen of the jejunum and was then made fast by tying these sutures. A few Lembert sutures were employed to approximate the jejunum and duodenum, thus avoiding undue tension on the sutures holding the pancreatic duct in the lumen of the jejunum.

RESULTS

Fourteen dogs were subjected to deviation of bile (fig. 2) by division of the common duct and anastomosis of the fundus of the gallbladder with the end-portion of the jejunum. Six dogs died in two weeks or less of shock or peritonitis. Eight dogs lived long enough to make them of experimental value; 1 is still alive and healthy after eleven months, 4 lived three months or longer, and 3 died one month after operation. Death was due in most instances to hepatitis or to pneumonia produced by migration of Dirofilariae from the heart into the lesser circulatory system whence they perforated to cause a hemorrhagic pneumonitis. In only 1 of the 8 dogs was an ulcer observed at autopsy. This ulcer occurred just distal to the pylorus and caused death of the animal in three months by a spontaneous healing which produced a duodenal stenosis. In all of the other animals the duodenal and gastric mucosa were apparently normal.

Eight dogs were subjected to deviation of the pancreatic juice (fig. 3) by transplantation of the pancreatic duct into the terminal portion of the jejunum. Three of the 8 dogs did not live long enough to be of experimental value, but the remaining 5 lived from two to four months.

Death was due to pneumonia produced by Dirofilariae. In none of the dogs was an ulcer observed, and in all instances the duodenal and gastric mucosa appeared grossly normal.

COMMENT

As Mann [36] had obtained experimental peptic ulcers of the duodenum in 20 per cent of dogs in which he had deviated the alkaline bile and pancreatic juice simultaneously to the lower intestinal tract, it was hoped that ulcers could be produced in the absence of one of the alkaline digestive juices (figs. 2 and 3). Had a fairly high incidence of duodenal ulcer occurred in the absence of either one of these alkaline digestive juices, some valuable information would have been obtained concerning the comparative protective value of either of them. The finding of a completely healed ulcer in the duodenum of 1 animal that was subjected to deviation of the bile does not justify drawing any conclusions concerning the comparative protective value of bile and pancreatic juice in preventing ulcer. The ulcer was merely an acute one which in the presence of pancreatic juice healed spontaneously. On the basis of the negative results obtained in this experiment one is probably justified in concluding that either bile or pancreatic juice alone does protect against ulcer formation. That the duodenal mucosa is highly resistant to ulcer formation is self-evident, especially when one considers that prompt healing occurred in the sutured defect caused by the "reaming" out of the pancreatic duct.

III. EFFECT OF ACID GASTRIC CHYME ON DUODENAL AND JEJUNAL MUCOSAE WHEN NEUTRALIZED BY BILE OR PANCREATIC JUICE ALONE

In this study experiments were carried out to determine the effect that bile or pancreatic juice, respectively, might have in the prevention of ulcer in duodenal and jejunal mucosae exposed to acid gastric chyme. Similar investigations had not previously been made. Bile and pancreatic juice, respectively, had been excluded by drainage to the outside or by ligating the common or pancreatic ducts, but their protective effects in either the duodenum or the jejunum had not been comparatively studied.

On the deviation of bile into the lower intestinal tract, pancreatic juice alone remained in the duodenum to counteract the corrosive action of acid gastric contents. Conversely, when pancreatic juice was deviated, bile remained alone to protect the duodenum.

When the foregoing deviations had been present long enough to be of experimental value, duodenal drainage was instituted. The jejunal loops which had formerly received bile (fig. 1) or pancreatic duct (fig. 4) transplantations were anastomosed to the antral end of the

stomach in order to determine the comparative protective values that either of the alkaline digestive juices might have in a jejunum exposed to the action of acid gastric chyme.

METHODS

Moderately large, well nourished dogs that had already become accustomed to kennel life were utilized, to lessen the risk of losing the animals before observations might be completed.

Deviation of Bile.—The common bile duct was identified and sectioned between mosquito forceps and a ligature placed just proximal to where the duct enters the duodenum. After the duct had been dissected free for 2 cm., two mosquito forceps were placed on the end of it, and between these the duct was split about 2 mm. upward. At a point on the jejunum about 30 cm. beyond the ligament of

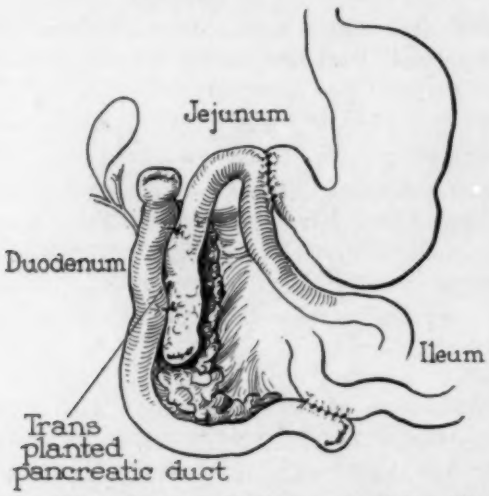

Fig. 4.—Drawing illustrating the duodenum containing bile drained into the ileum and substitution for it of the jejunum containing the transplanted pancreatic duct.

Treitz sutures were placed as in study II, and the duct was drawn through a stab wound into the lumen of the jejunum and secured. A few Lambert sutures were placed to approximate the jejunum and duodenum to lessen undue tension of the transplant. The loop of jejunum utilized was placed so that it ran upward and parallel to the duodenum in order that it might satisfactorily serve for the second part of this study.

Deviation of Pancreatic Juice.—This was accomplished as in study II, except that the transplant was made in the jejunum at a point 30 cm. beyond the ligament of Treitz.

Substitution of Jejunum Containing Transplant for Duodenum (figs. 4 and 5).—After the animals subjected to the two preceding transplantations had served their purpose they were reoperated on. The stomach was sectioned proximal to the pylorus and the end of the duodenum with the attached pars pylorica was closed with through and through and Lembert sutures. Next the jejunum was sectioned

a few centimeters below the duct transplant. The end leading up to the transplant was closed, and the proximal or duodenal end was anastomosed into the distal portion of the ileum. The loop of jejunum containing the transplant was placed so that it led up into the upper right quadrant of the abdomen and then turned downward so that its antimesenteric border could be anastomosed, end-to-side, with the stomach. The latter anastomosis was accomplished with continuous silk sutures for both the mucosa and the serosa (figs. 4 and 5).

Immediately following operation the dogs received an infusion and were subsequently fed in the same manner until the sixth day. They were then given dextrose and milk until the ninth day, when they were placed on regular kennel rations.

RESULTS

After transplantation of either the common or the pancreatic duct the dogs were allowed to go from twenty-three to fifty-two days (aver-

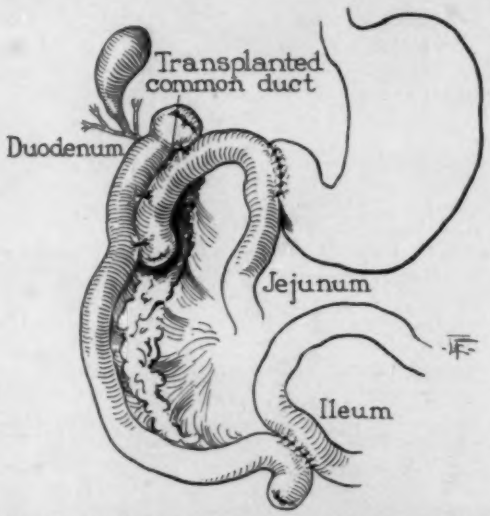

Fig. 5.—Drawing illustrating the duodenum containing pancreatic juice drained into the ileum and substitution for it of the jejunum containing the transplanted common duct.

age of thirty-five days) before they were subjected to the second operation. Twelve dogs were subjected to reoperation, and in neither group of 6 each was a duodenal ulcer found on exploration. Likewise there were no ulcers in 2 additional dogs, 1 from each group, that died four weeks and one week after the original operation. In these 14 dogs the failure of ulcers to form in the duodenum substantiates the results obtained in study II and increases the number of dogs subjected to deviation of bile to 15 and to deviation of pancreatic juice to 12.

Of the 7 dogs on which transplantation of the common duct had been performed, 6 were reoperated on from twenty-one to fifty-one days later (average of thirty days). After "surgical duodenal drainage" (fig. 5) or excluding the duodenum and substituting the jejunum

Fig. 6.—Photograph showing a huge callous ulcer and two smaller chronic ones obtained in a jejunum protected by bile alone.

Fig. 7.—Photograph showing an ulcer that had perforated and four smaller ones obtained in a jejunum protected by bile alone.

with its common duct transplant, 1 dog died of pneumonia on the tenth day. No ulcer was present, but erosion was evident about the silk sutures. The five remaining dogs all died in from twenty-two to fifty days with ulcers of the jejunum that had either perforated or caused a fatal hemorrhage. Most of the ulcers occurred within 2 cm. of the gastrojejunostomy, and all were of the chronic type seen in man. In an animal that bled to death a callous ulcer measuring 4 by 5 cm. had caused adhesions to a neighboring loop of intestine. Distal to this huge

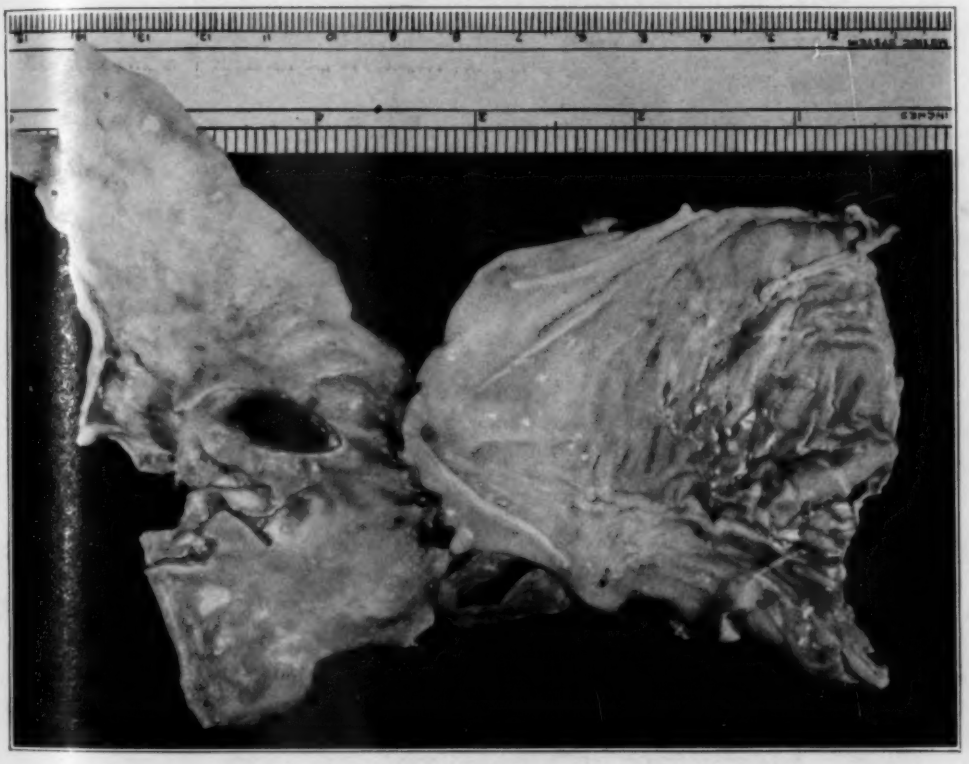

Fig. 8.—Photograph showing a perforating ulcer obtained in a jejunum protected by bile alone.

ulcer were two smaller chronic ones (fig. 6). In another animal in which the ulcer perforated there were four smaller chronic ones further down in the jejunum (fig. 7). In the other 3 animals, in addition to a large perforating ulcer, there were also one or two small chronic lesions.

Of 7 dogs on which transplantation of the pancreatic duct had been performed, 6 were reoperated on. After the duodenum had been excluded and the jejunum with its pancreatic duct transplant (fig. 4) substituted, 1 dog died with pneumonia on the eighth day without an

ulcer. The 5 remaining dogs all died in from fourteen to forty days with ulcers, three of which perforated (fig. 8) and two of which caused a fatal hemorrhage (fig. 9). All of the ulcers were of the chronic type and occurred within 1 cm. of the gastrojejunostomy, being multiple in only 1 dog. In this animal there were two additional small callous ulcers.

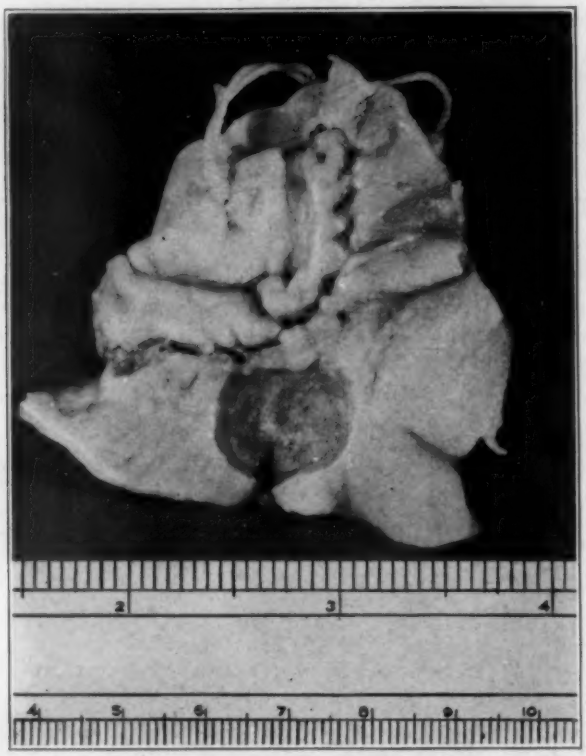

Fig. 9.—Photograph showing a superficial ulcer obtained in jejunal mucosa protected by pancreatic juice alone.

COMMENT

In 14 dogs, common duct and pancreatic duct transplantations which deprived the normal duodenum of one or the other of the alkaline digestive juices were not followed by the occurrence of peptic ulcers, as was also shown in study II. In the former study bile was deviated by anastomosing the fundus of the gallbladder into the ileum, because this seemed technically easier than transplanting the common duct iself. However, the converse has proved easier, and it is not attended by hepatitis from retrograde filling of the gallbladder by intestinal contents.

Following transplantation of the common duct, for example, the pancreatic juice remained to protect the duodenal mucosa, but following the second operation ("duodenal drainage"; fig. 5) there was only bile to protect the jejunum substituted for the duodenum. In the other group of dogs the converse was true (fig. 4). The fact that peptic ulcers caused fatalities in all of the 5 dogs in each group that lived long enough for experimental purposes proves that the jejunal mucosa is more sensitive to the formation of peptic ulcer than is the duodenal mucosa. It was hoped that pancreatic juice could be definitely shown to be more protective than bile, but the results merely suggest this. The ulcers that occurred in the jejunum protected by pancreatic juice were actually not so large (fig. 8), not so prone to perforate (fig. 9) (three perforated) and not so often multiple (1 dog with multiple ulcer) as were those that occurred when bile was deviated to protect (four ulcers perforated, and in all dogs there were multiple ulcers; figs. 6 and 7). That neither of the alkaline digestive juices can prevent the formation of ulcers in jejunal mucosa exposed to the corrosive action of acid gastric chyme is definitely demonstrated in these experiments.

SUMMARY AND CONCLUSIONS

When "duodenal drainage" was performed and alkaline duodenal contents were deviated into the stomach just proximal to the pyloro-jejunal anastomosis (experiment I) ulcers did not form. This indicates that the neutralization of acid gastric chyme as it passed through the pylorus prevented the formation of ulcers. It does not substantiate the belief of McCann [3] that trauma is of great importance in the production of ulcers following "duodenal drainage."

If either bile or pancreatic juice was deviated from the duodenum into the lower intestinal tract (experiments II and III) the remaining duodenal contents were sufficient in quantity and alkalinity to prevent ulceration of the duodenum.

After the performance of "duodenal drainage" and transplantation of either the common bile duct or the pancreatic duct into the jejunum near the pylorojejunal anastomosis (experiment III) chronic or perforating peptic ulcers formed in all instances. The characters of the ulcers suggested that pancreatic juice may be more protective than bile.

CHRONIC ULCERATIVE COLITIS WITH ASSOCIATED CARCINOMA

PROGRESS IN MANAGEMENT

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AND
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In 1928, one of us (Dr. Bargen)[1] reported nineteen cases encountered at the Mayo Clinic in which a malignant neoplasm was associated with a lesion of long-standing, chronic ulcerative colitis and one case of lymphatic leukemia associated with progressive, fulminating, chronic ulcerative colitis. In three of the nineteen cases proof of a malignant condition lay in the development of a large filling defect in the colon, with a sudden and rapid change of symptoms and with signs of obstruction, cachexia and anemia; in fourteen cases a specimen removed either at operation or at necropsy established the diagnosis of carcinoma, and in two cases, the diagnosis of lymphosarcoma.

The cases in this series had many striking features in common. The sudden change in symptoms, the rapid failure of the patients, the apparent futility of treatment and the early demise of the patients were noteworthy. Of the twenty patients only one who underwent resection of the diseased portion of the colon for carcinoma and only one who underwent resection of a large section of the bowel for lymphosarcoma are living today. All of the rest died within from several days to several months after discovery of the malignant process. Most of them died within several weeks, irrespective of the treatment employed.

Polypoid hyperplasia of the inflamed mucous membrane was noted when the patients came under observation prior to the development of actual malignant disease. In more than a third of the cases polyps were found in the rectum at the time of proctoscopic examination before carcinoma appeared. We made a detailed report[2] of this association of polyps and chronic ulcerative colitis in 1930 and found polyps in 10 per cent of all of the cases of long-standing chronic ulcerative colitis. If polyps occur subsequently, therefore, in 10 per cent of cases of chronic ulcerative colitis and if in more than 60 per cent of the cases

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From the Division of Medicine and the Division of Surgery, the Mayo Clinic.

1. Bargen, J. A.: Chronic Ulcerative Colitis Associated with Malignant Disease, Arch. Surg. **17**:561 (Oct.) 1928.

2. Bargen, J. A., and Comfort, M. W.: The Association of Chronic Ulcerative Colitis and Multiple Polyps, Ann. Int. Med. **4**:122 (Aug.) 1930.

in which carcinoma develops later the patient has passed through the stage of polyposis, it seems that the presence of polyps and the destructive infection of this type of colitis may predispose to carcinoma. Proof of this is lacking, but a study [3] in 1933 strongly suggested the presence of a neoplastic factor in chronic ulcerative colitis. Because of this, a further review of the cases reported in 1928 and some observed since then was undertaken to see if the newer clinical data might add information of value from the therapeutic standpoint.

The present study concerns twenty-five cases of carcinoma and two of lymphosarcoma proved at pathologic examination, the tumor developing in the course of severe chronic ulcerative colitis. The cases of the former report are included here, but they are considered principally from the standpoint of management. Of the twenty-seven patients, twelve were women and fifteen were men. The ages of the patients at the time of discovery of the carcinoma ranged from 21 to 69 years. In the cases of the younger patients the history of colitis was particularly likely to be long, and many of them had presented clinical and pathologic evidence of colitis for years.

A sudden change of symptoms with unusual bleeding and local pain in patients who had been under repeated observation was considered to be indicative of the onset of carcinoma. No one knows how long it takes a subclinical carcinoma to assume symptomatic proportions, but judging from the fulminating course of the disease after the change in symptoms and from the actual observation of pathologic change, the history of carcinoma is probably fairly accurately represented by the time given in table 1.

In case 1, the diagnosis of ulcerative colitis was established by proctoscopic examination as early as 1915, when the patient was 9 years of age. Since little encouragement could be given, the patient was not seen at the clinic again until 1924. In these nine years the trouble had slowly progressed, with numerous fulminating exacerbations of symptoms and some periods of partial recovery. A proctoscopic and roentgenologic examination in 1924 confirmed the diagnosis of advanced, destructive colitis. At that time treatment with vaccine, prepared from diplostreptococci isolated from the patient's rectal ulcers, was begun, and improvement followed rapidly. The patient gained weight and was soon engaged in a wage-earning occupation. Proctoscopic examinations in 1926 and in January and April 1927 revealed healed colitis. Early in December 1927 there was a slight recurrence, and proctoscopic examination disclosed the typical picture of chronic ulcerative colitis. The

3. Brust, J. C. M., and Bargen, J. A.: The Neoplastic Factor in Chronic Ulcerative Colitis, New England J. Med. **210**:692 (March 29) 1934.

Summary of Data in Twenty-Seven Cases

Case	Year of First Admission	Age on First Admission, Years	Time Under Observation at Mayo Clinic	Chronic Ulcerative Colitis: Time from First Symptom to First Examination at Clinic	Chronic Ulcerative Colitis: Extent, Grade*	Time Polyposis Present Before Carcinoma Appeared	Carcinoma: Age When First Appeared, Years	Carcinoma: Time from First Symptom to Discovery at Examination	Carcinoma: Time from First Symptom to Death	Carcinoma: Situation	Carcinoma: Basis for Final Diagnosis	Comment
1	1915	9	9 years	3 years	4	Yes	21	20 days	3 months	Rectum	Proctoscopy and biopsy	
2	1924	11	8 years	2 years	3	Yes	21	3 weeks	5 weeks	Cecum	Necropsy	
3	1925	26	1 year	10 years	4	Yes	26	3 weeks	6 weeks	Entire colon	Necropsy	
4	1933	30	1 week	8 years	2	No	30	2 weeks	.....	Rectum	Resection	From first symptoms to extirpation, nearly 3 months; alive after initial symptom, 7 months
5	1927	32	2 months	8 years	3	No	32	3 months	5 months	Cecum	Biopsy	
6	1916	19	9 years	11 years	3	No	28	5½ months	6 months	Transverse colon	Necropsy	
7	1927	33	2 years	14 years	4	Yes	35	3 months	4½ months	Rectum and cecum	Biopsy	
8	1924	43	2 weeks	25 years	3	Yes	43	2 weeks	1 month	Sigmoid and splenic flexure	Resection	
9	1916	39	11 years	16 years	3	Yes	50	3 months	5 months	Rectum (multiple growths)	Biopsy	
10	1929	47	4 months	18 years	3	Yes	47	4 months	4 months	Transverse colon	Resection	Died 48 hours after resection
11	1917	38	1 year	19 years	3	Yes	38	3 months	3 months	Splenic flexure and descending colon	Necropsy	Died 3 days after ileostomy
12	1916	53	1 year	23 years	Unknown	Yes	56	Unknown	.....	Unknown	Necropsy	Died at home; interval unknown
13	1919	43	2 years	2 years	3	Yes	43	9 months	9 months	Transverse colon	Necropsy	
14	1922	60	1 day	9 months	3	No	60	Unknown	.....	Sigmoid	Necropsy	Died of perforation of colon after cecostomy
15	1925	57	2 weeks	1 year	3	No	57	Unknown	.....	Hepatic flexure	Necropsy	Died of perforation of colon after cecostomy
16	1926	63	8 months	1½ years	3	Yes	63	2 months	8 months	Cecum	Necropsy	
17	1927	55	3 days	9 months	Unknown	No	55	Unknown	.....	Descending colon	Necropsy	Died at home; interval unknown
18	1931	69	3 days	1¼ years	1	No	69	6 weeks	6 weeks	Hepatic flexure	Necropsy	Died of peritonitis after ileosigmoidostomy
19	1919	60	4 weeks	1½ years	1	No	60	6 weeks	.....	Rectum	Resection	Died at home; interval unknown
20	1925	45	3 months	7 years	1	Yes	45	2 months	3 months	Anus to splenic flexure (multiple growths)	Biopsy	Died after colostomy
21	1924	40	2 months	2 years	3	No	40	Unknown	.....	Cecum	Necropsy	Died at home; interval unknown
22	1931	45	1 week	11 years	1	Yes	45	6 months	.....	Anus to splenic flexure (multiple growths)	Biopsy	Died at home; interval unknown
23	1925	65	1 year	35 years	1	No	65	3 months	.....	Sigmoid	Resection	From first symptom to extirpation, 3 months; alive after initial symptom, 8 years
24	1932	40	5 years	10 years	3	Yes	40	Unknown	.....	Rectum	Biopsy	Alive after initial symptom, 10 years
25	1927	32	2 years	7 years	3	Yes	34	Unknown	.....	Rectum	Biopsy	Alive after initial symptom, 6 months
26	1923	46	1 year	6 years	3	Yes	46	3 months	.....	Cecum	Resection	From first symptom to extirpation, 4 months; alive after initial symptom, 5 years
27	1929	53	4 years	7 years	1	Yes	57	2½ months	.....	Rectum	Biopsy	From first symptom to extirpation, 3½ months; died 8 days after resection

* Grade 4 indicates involvement of the entire colon and the terminal portion of the ileum; grade 3, the entire colon; grade 2, the anus to the hepatic flexure, and grade 1, the anus to the splenic flexure.

condition grew progressively worse, and proctoscopic examination on Jan. 3, 1928, revealed hyperplasia of the mucosa in several places, with an indurated ridge measuring 2 by 5 cm., about 8 cm. from the anus. A specimen of tissue removed from this region was reported as being adenocarcinoma, grade 4. Radium applied locally caused shrinkage of the lesion and an apparent beneficial effect on the mucosa generally. However, improvement was only temporary; the patient began to fail rapidly and died less than five months after the first appearance of the malignant change.

Fig. 1 (case 20).—Roentgenogram showing chronic ulcerative colitis involving the colon distal to the middescending segment. Examination revealed that this entire segment was densely infiltrated with carcinoma as well.

Data on some of the early cases are not complete, but in eighteen of the twenty-seven cases the entire colon was involved by severe, advanced destructive colitis. In recent years the malignant progress of carcinoma has been graded. In six of these cases the lesion was graded 4; in one, 3, and in five, 2. In cases 3, 9, 20 and 22, the intestines were stiff, carcinomatous tubes as far cephalad as they could be examined (fig. 1). In several other cases multiple disseminated carcinomas were present, and in still others there was chronic ulcerative colitis involving the entire colon associated with a single carcinomatous portion (figs. 2 and 3 and table).

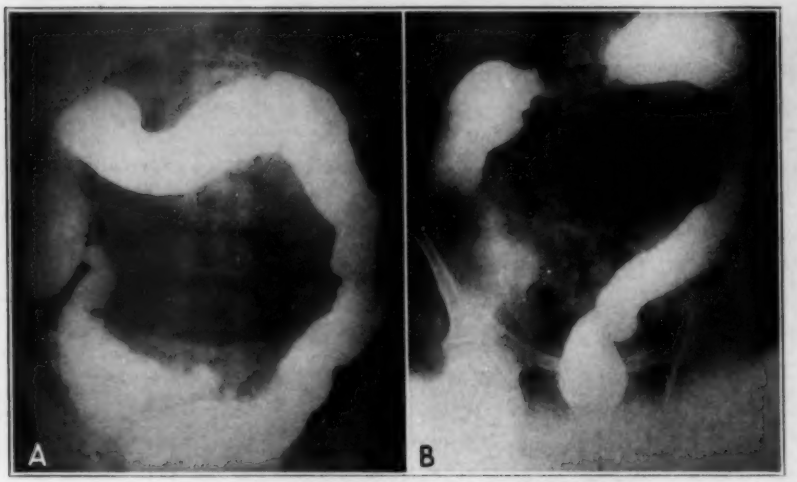

Fig. 2 (case 6).—Rcentgenograms showing: *A*, the colon typically involved by chronic ulcerative colitis (taken in 1916); *B*, the carcinomatous defect in the midtransverse colon.

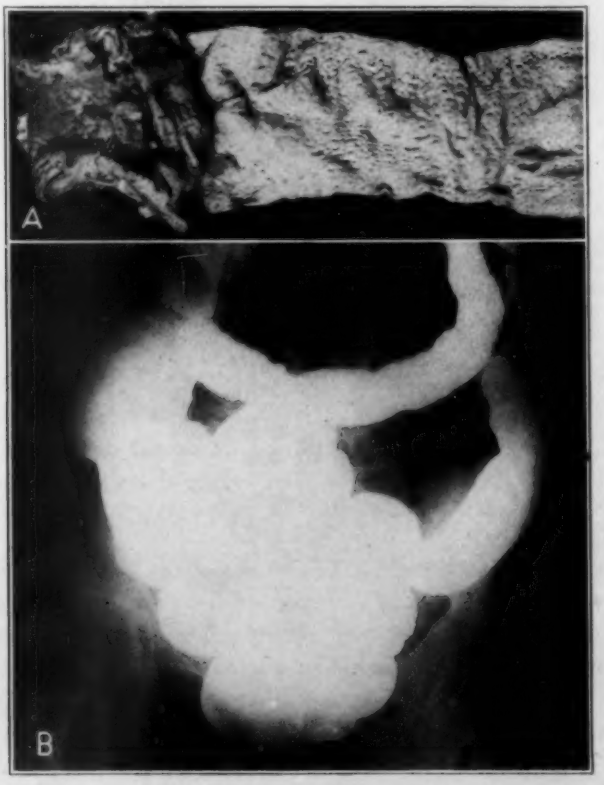

Fig. 3 (case 10).—*A*, photograph of a single carcinoma with chronic ulcerative colitis. *B*, roentgenogram showing a stricture-like defect of the transverse colon near the hepatic flexure.

These statistics suggest a rather hopeless outlook for the patient with chronic ulcerative colitis in whom colonic carcinoma develops. In general, this may be true, but some striking exceptions are to be found. Two of the seven new cases, reports of which have not hitherto been published, are here reported in detail. These are cases 4 and 27 in the table.

REPORT OF CASES

CASE 4.—A man, aged 30, came to the clinic on Sept. 15, 1933, complaining of chronic ulcerative colitis of eight years' duration. In July 1925, during his

Fig. 4 (case 4).—Roentgenogram showing chronic ulcerative colitis involving the colon from the anus to the splenic flexure.

first episode of bloody dysentery, he had averaged thirty rectal discharges daily. His weight had gone from 210 to 147 pounds (95.3 to 66.7 Kg.) within eight weeks. The trouble had continued in the main without remission, although there had been short periods of improvement, such as those which occurred in 1932 and 1933, when his weight had reached 188 pounds (85.3 Kg.) and when the bowel movements had become reduced to five or six every twenty-four hours. During this year treatment was for a diplostreptococcic type of colitis. On Sept. 1, 1933, he had had a peculiar intermittent throbbing sensation in the rectum, with a sense of rectal blockage. At that time diarrhea had increased. He had consulted the physician at his home, and proctoscopic examination had revealed carcinoma of the rectum on an inflammatory base.

On admission the patient's general condition was good. The value for hemoglobin was 15.2 mg. per hundred cubic centimeters of blood; the erythrocytes numbered 4,180,000, and the leukocytes, 11,700, per cubic millimeter of blood. Of the leukocytes, 73 per cent were polymorphonuclear neutrophils. A roentgenogram of the thorax showed nothing abnormal. Sigmoidoscopic examination revealed a tube from 1 to 2 cm. in diameter which was contracted for 24 cm. Just above the anus and involving the inner margin of the posterior and left wall of the rectum was an irregular superficial, nodular lesion measuring about 2 by 2 cm. A specimen of tissue revealed adenocarcinoma, grade 2. A roentgenogram disclosed evidence of chronic ulcerative colitis distal to the middle of the transverse colon, with extreme narrowing of the distal segments (fig. 4).

Fig. 5 (case 4).—Photograph of the descending colon and the rectum. The carcinoma may be readily identified in the rectum; the bowel is extensively ulcerated and contracted.

The patient was given a short course of treatment with a solution of the specific antibodies and intraperitoneal injections of vaccine made from streptococci and colon bacilli, and on September 22 the abdomen was explored through an upper left rectus incision. There were no hepatic metastatic growths. The right half of the colon seemed normal. The remainder of the colon, beginning just proximal to the splenic flexure, was contracted, thick-walled and ropelike—its appearance being

grossly typical of that in chronic ulcerative colitis. The transverse colon was divided at its median point; the end of the distal segment was closed and covered with omentum, and the distal end of the proximal portion was utilized for the single-barreled type of colostomy. Postoperative convalescence was somewhat stormy because of the development of bilateral parotitis, but this was effectively treated by the use of surface packs of radium. The patient was allowed to return home for a few weeks.

The patient returned to the clinic on November 18. His general condition was much improved, and he had gained 12 pounds (5.4 Kg.). On November 21, the entire portion of the colon distal to the colonic stoma and rectum was removed (fig. 5). Recovery was uneventful. On Feb. 6, 1934, two and one-half months later, the patient reported that his weight and strength were normal and that he had resumed his usual duties as operator of an oil station. A similar report was made five months after operation.

Surgical treatment in this case was a formidable undertaking. A surgical procedure of somewhat less magnitude could have been chosen had we been dealing with a malignant disease only of the rectum, but a malignant process superimposed on an intractable chronically ulcerated bowel presents a different problem. If the diseased segment of bowel is resected in such cases, the result is unsatisfactory, and frequently the patient dies. If a colonic stoma had been made in the descending colon in this case, and if recovery from operation had followed, the result still would have been unsatisfactory. Occasionally a colonic stoma is seen in an extensively ulcerated colon. In these cases the colonic stoma is usually so contracted and small that elimination is inadequate and general debilitation from the disease is not lessened. Obviously, in such cases, another stoma has to be made in healthy bowel proximal to the diseased segment.

In such a case as the foregoing, then, if any surgical procedure is to be carried out, the entire diseased segment should be removed. If only inflammatory disease had been present, obviously an ileostomy or a colostomy alone would have been resorted to, which in some cases of intractable, chronic ulcerative colitis with other complications is sufficient. Occasionally, however, it becomes necessary to remove the diseased colon in such cases because of general debilitation due to the presence of an overwhelming infection.

Case 27.—An unmarried woman, aged 53, came to the clinic on May 6, 1929, with a history of chronic ulcerative colitis of three years' duration. There had been many bloody purulent rectal discharges. Proctoscopic examination at that time revealed the usual granular, easily bleeding mucous membrane. Diplostreptococci were isolated from the rectal lesions. The patient was given a solution of the specific antibodies followed by some vaccine; during the succeeding months her improvement was satisfactory. When the colitis began to improve, she mentioned that she had had menorrhagia for a year; dilatation and curettage revealed adenocarcinoma, grade 1, of the fundus of the uterus. On June 1, 1929, total abdominal hysterectomy was performed. Recovery from both procedures

was satisfactory, so that she was able to return to her teaching. She made frequent reports by mail and as late as Aug. 15, 1933, she reported that she was in excellent condition. However, on Jan. 1, 1934, she stated that she had had recurring cramping pain in the left lower abdominal quadrant. The first attack had occurred in November, and by the time of her return to the clinic, on Feb. 1, 1934, she had had five or six attacks suggestive of an obstructive lesion. Digital examination revealed an annular lesion on an inflammatory base, in the lower portion of the sigmoid flexure; this lesion had narrowed the lumen to such an extent that it did not admit the index finger. The walls of the rectum were somewhat fibrous, but more flexible than they had been. A specimen removed from the lesion revealed adenocarcinoma, grade 2. The mucous membrane of the rectum below the lesion appeared normal as viewed through the proctoscope.

On February 6, exploration was made through a left rectus incision. Palpation of the liver did not reveal metastatic growths. The aortic lymph nodes were not palpable. Examination of the entire colon, beginning at the cecum, was carried out. The walls of the bowel were normal to palpation, in contrast to the typically ropelike colon found in ulcerative colitis. Exploration of the pelvic portion of the sigmoid revealed a rounded mass, evidently a carcinoma. The lower borders of the growth extended to within 5 cm. of the pelvic peritoneal fold. The growth was movable. A colonic stoma was made in the middle of the descending colon in anticipation of a second surgical procedure at the time at which the neoplasm was to be resected. Convalescence following this first procedure was satisfactory.

Four weeks later a second operation was carried out through an abdominal incision low in the median line. Segmental resection of the lower portion of the sigmoid was performed, and an end-to-end anastomosis was made (fig. 6). After the procedure was completed, a large rectal tube was passed through the colonic stoma into the distal segment of the bowel, beyond the anastomosis and into the lower portion of the rectum. The immediate convalescence was satisfactory. On the sixth postoperative day the patient's temperature became elevated to 104 F., with marked acceleration of the pulse rate. Death occurred two days later, on the eighth postoperative day. Clinically, the cause of death was peritonitis, and this impression was corroborated at necropsy. Distant metastatic growths were not found.

In the last two years one of us (Dr. Dixon) has carried out eight operations of this sort for growths in the lower part of the sigmoid flexure; seven of the patients recovered. Was the presence of long-standing chronic ulcerative colitis a factor which enhanced the development of peritonitis? To any one who has carried out abdominal operations on patients suffering from chronic ulcerative colitis it is apparent that fulminating peritoneal infection is not uncommon, and even though in the case in point there had been marked symptomatic relief from colitis, it seems possible that some residual infection still remained in the wall of the bowel.

Intraperitoneal vaccination carried out preoperatively has reduced the mortality rate from peritonitis appreciably. If peritonitis develops, however, it is usually of an overwhelming type, as it was in this case, and the causative organism is usually a streptococcus.

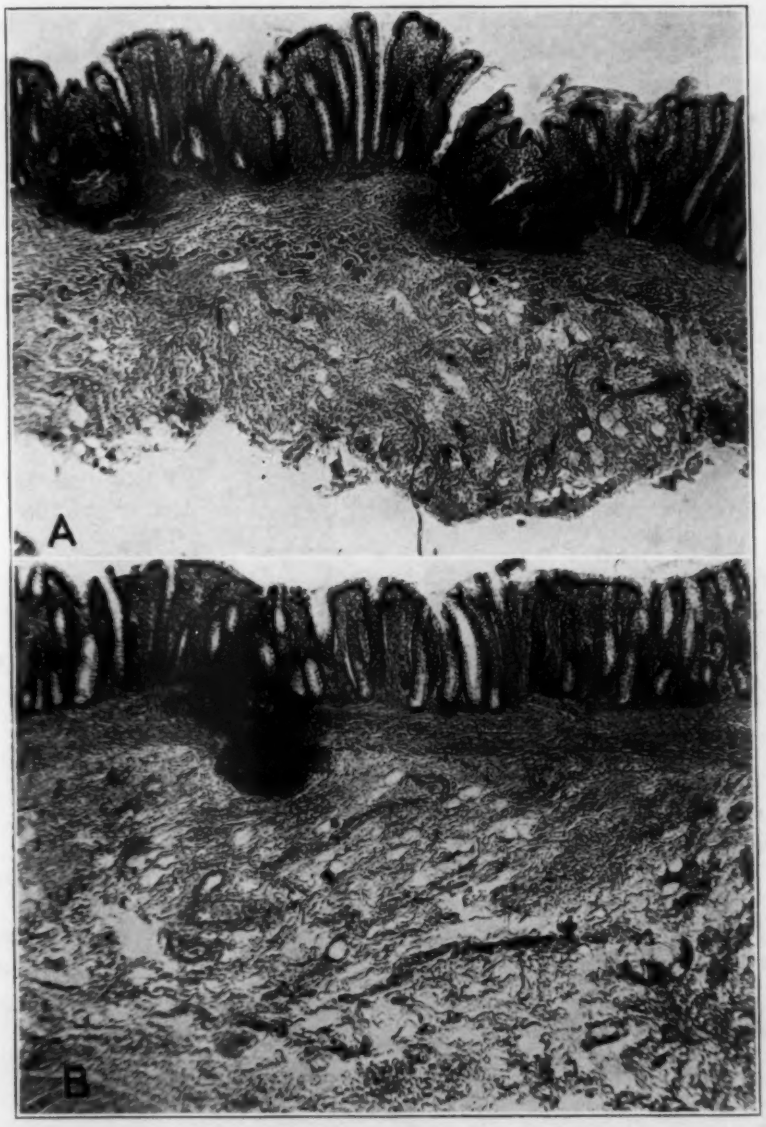

Fig. 6 (case 27).—*A*, photomicrograph of a section of the wall of the colon just above the growth. *B*, photomicrograph of a section of the rectum below the growth. The comparatively adequate wall which resulted after the healing of the chronic ulcerative colitis may be noted.

COMMENT

So far, no satisfactory treatment for diffuse colonic carcinomatosis, such as was present in cases 3, 9, 20 and 22, is at hand, nor have we any satisfactory treatment for the higher grades of carcinoma associated with this form of colitis. However, for localized, relatively early carcinoma of grades 1 and 2, in cases in which colitis is under fair control, radical extirpation of the diseased colon with the carcinoma offers the patient a good chance of recovery.

It should be stated that in cases 24 and 25 polypoid excrescences in the rectum were fulgurated when the colitis was under control, and this treatment alone has been adequate so far, since the small carcinomas have not recurred. This suggests the importance of prompt proctoscopic observation with any change in symptoms. It also emphasizes the importance of grading specimens removed for biopsy. These two specimens were the only ones in the series recorded as showing malignancy of grade 1.

One is again confronted, and in a most dramatic manner, with the hopelessness, in all probability, of rapidly developing carcinoma among younger persons. In general, in these cases the younger the patient, the more likely it is that the disease will be of the fulminating type and the carcinoma multiple and of a high grade of malignancy.

An attempt to resect the growth locally when active, or even quiescent, colitis is present seems futile. It seems best to resect the entire section of the colon involved by colitis and containing one or more carcinomas. It seems more than accidental that the five surviving patients had adequate treatment with specific antibody solution (concentrated serum) or vaccine prepared from the diplostreptococci of chronic ulcerative colitis, or both, prior to any attempted surgical procedure and that in each case the active stage of colitis was under control when surgical intervention was undertaken. Contrasted with this, only seven of the twenty-two patients who died were given serum or vaccine, and only three of them to the point of control of symptoms. We gained the impression, through close observation, that in these three cases as healing took place the factor responsible for the healing lost control and the mucosa grew wildly as new hyperplastic tissue.

HEPATIC FUNCTION

III. THE EFFECT OF CHOLECYSTECTOMY ON HEPATIC FUNCTION

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AND

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PHILADELPHIA

Considerable attention has been directed toward the morphologic changes which occur in the biliary system following surgical removal of the gallbladder. There are, however, practically no data available regarding the effect of cholecystectomy on the functional efficiency of the liver. At first it seems improbable that mere removal of the gallbladder should exert any deleterious effect on hepatic function. However, every surgeon of experience in this field has encountered instances of serious postoperative morbidity and even death following simple cholecystectomy in patients who were apparently in good condition before operation. A variety of factors are involved in the production of many of these postoperative calamities, e. g., anesthesia, undetected hepatic damage, renal complications, operative trauma and shock. In certain cases, however, the most careful preoperative study fails to reveal any significant hepatic or renal functional impairment; cholecystectomy is performed with no undue trauma; anesthesia, general, spinal or local, is apparently free from untoward effects, and still the patient promptly shows evidence of profound functional disturbance, particularly of the liver and kidneys, and may die within a few days after operation.

In an attempt to investigate the pathogenesis of these postoperative phenomena we have been studying patients with disease of the biliary tract before, and at frequent intervals after, operation. In the present report we shall review our observations with regard to the concentration of serum bilirubin and the retention of bromsulphalein in a series of sixty patients with cholecystitis, without clinical jaundice, on whom simple cholecystectomy was performed.

EXPERIMENTAL DATA

As stated earlier, no patient in this series was clinically jaundiced; gallstones, when present, were confined to the gallbladder. Simple cholecystectomy was performed in each case with the patient under nitrogen monoxide and ether, infiltration or spinal anesthesia. In no case was the common duct manipulated or other operative procedure car-

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ried out. All the patients were in good clinical condition before and during operation, and there were no fatalities.

The serum bilirubin was determined by the quantitative van den Bergh procedure as modified by Thannhauser and Andersen. As stated in a previous report,[1] the normal range of serum bilirubin, according to our experience, is from 0.1 to 1 mg. per hundred cubic centimeters; in about 50 per cent of the persons the serum bilirubin falls below 0.5 mg.,

TABLE 1.—*Data for Patients Showing No Preoperative Hyperbilirubinemia or Retention of Dye*

Patient	Serum Bilirubin, Mg. per 100 Cc.		Retention of Dye, Percentage	
	Before	After	Before	After
L. F.	0.40	0.76	0	0
A. L.	0.50	0.90	0	10
A. An.	1.00	0.90	0	0
E. Ti.	0.40	0.26	0	0
L. C.	0.62	0.86	0	0
I. B.	0.90	1.30	0	0
T. Y.	0.72	0.86	0	0
A. S.	0.70	1.10	0	10
E. Le.	0.85	1.20	0	0
A. Ab.	0.80	1.20	0	10
E. Lei.	0.65	0.84	0	0
J. D.	0.57	0.74	0	0
M. M.	0.60	0.90	0	10
M. G.	0.72	0.98	0	0
T. M.	0.48	0.72	0	0
H. McA.	0.48	0.75	0	10
J. C.	0.37	0.62	0	0
F. R.	0.92	0.90	0	20
A. M.	0.36	0.64	0	0
A. DeC.	0.60	1.20	0	10
S. S.	0.72	0.74	0	10
B. Z.	0.52	1.09	0	20
R. H.	0.55	0.36	0	30
M. R.	0.76	1.40	0	0
J. R.	0.52	1.10	0	25
M. K.	0.41	0.70	0	10
S. B.	0.32	0.40	0	20
A. Ca.	0.50	0.70	0	15
S. V.	0.65	0.90	0	0
L. V.	0.80	0.42	0	0
M. Sm.	0.68	0.32	0	0
C. W.	0.56	1.08	0	0
M. Sh.	0.40	0.60	0	0
M. H.	0.39	0.72	0	0
S. B.	0.35	0.65	0	0
L. C.	0.11	0.12	0	0
S. R.	0.30	0.60	0	20
C. M.	0.70	0.60	0	50
M. M.	0.43	0.23	0	0
A. K.	0.80	0.36	0	0
C. C.	0.68	0.46	0	0

and in about 95 per cent it fell below 0.8 mg. Bromsulphthalein was administered in the dosage of 2 mg. per kilogram of body weight, the degree of retention being determined at the end of thirty minutes.

Several studies were made in the majority of instances; the two figures reported here are those obtained within twenty-four hours before and twenty-four hours after cholecystectomy. No morphine was administered to any patient in this series between the time of operation and the reported postoperative observations.

1. Cantarow, A.: Hepatic Function: I. Noncalculous and Calculous Cholecystitis, Arch. Int. Med. **54**:540 (Oct.) 1934.

In order to simplify the analysis of the experimental data, the patients may be divided into several groups in accordance with observations made before operation.

Patients with No Preoperative Hyperbilirubinemia or Retention of Dye.—There were forty-one patients who before operation showed neither hyperbilirubinemia nor retention of bromsulphalein after thirty minutes. The detailed findings are presented in table 1. A significant increase in the concentration of serum bilirubin twenty-four hours after

TABLE 2.—*Data for Patients Showing Preoperative Hyperbilirubinemia or Retention of Dye*

Patient	Serum Bilirubin, Mg. per 100 Cc.		Retention of Dye, Percentage	
	Before	After	Before	After
M. R.	2.00	1.30	10	10
R. M.	0.65	0.70	5	0
M. C.	0.90	1.40	5	10
E. F.	0.80	1.60	10	20
P. S.	0.70	0.85	5	15
M. P.	0.70	0.92	5	20
J. A.	0.80	0.92	25	60
J. M.	0.70	0.75	5	0
F. C.	2.40	0.90	0	0
E. T.	0.80	0.40	100	5
F. G.	1.20	0.50	0	10
M. L.	1.10	0.58	0	10
J. R.	1.10	2.24	0	15
T. F.	1.36	1.26	15	0
A. Cu.	0.44	3.76	5	30
L. A.	1.20	0.90	0	0
E. M.	2.24	0.63	45	5
M. L.	2.40	3.60	15	55
J. H.	0.75	0.92	5	10

TABLE 3.—*Summary of Data for Patients with No Preoperative Retention of Dye*

Cases	Serum Bilirubin				Retention of Dye		
	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased
46	0.11-2.40	0.12-2.24	27 (60%)	13 (28%)	0	0-50	19 (41%)

cholecystectomy occurred in twenty-six cases (63.4 per cent), the value being above the upper limit of normal (1 mg.) in nine instances (21.9 per cent). An abnormal degree of retention of dye (from 10 to 50 per cent) was noted twenty-four hours after operation in sixteen cases (39 per cent).

There was no apparent relation between the postoperative increase in serum bilirubin and the retention of dye. Of the sixteen patients in whom retention of dye occurred, two showed decrease in the concentration of serum bilirubin (R. H. and C. M., table 1). Furthermore, these two patients exhibited the most marked degree of retention of dye observed in this group (30 and 50 per cent). In five instances reten-

tion of dye was accompanied by no significant alteration in the degree of bilirubinemia.

Patients with Preoperative Hyperbilirubinemia or Retention of Dye.—There were nineteen patients who showed some degree of either hyperbilirubinemia or retention of dye before operation. The detailed findings are presented in table 2. Since the significant findings in this group will be referred to later, it is not necessary to review them at this point; we merely point out again the apparent lack of consistent correlation between the degree of bilirubinemia and the retention of dye.

TABLE 4.—*Summary of Data for Patients with Preoperative Retention of Dye*

	Serum Bilirubin				Retention of Dye			
Cases	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased	Decreased
14	0.44-2.40	0.40-3.76	8 (57%)	4 (28%)	5-100	0.55	8 (57%)	2 (36%)

TABLE 5.—*Summary of Data for Patients with No Preoperative Hyperbilirubinemia*

	Serum Bilirubin				Retention of Dye			
Cases	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased	Decreased
51	0.11-1.00	0.12-3.76	33 (66%)	10 (20%)	0-100	0-50	23 (45%)	3 (6%)

TABLE 6.—*Summary of Data for Patients with Preoperative Hyperbilirubinemia*

	Serum Bilirubin				Retention of Dye			
Cases	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.	Increased	Decreased	Before	After	Increased	Decreased
9	1.10-2.40	0.50-3.60	2 (22%)	7 (78%)	0-45	0-55	4 (44%)	2 (22%)

Patients with No Preoperative Retention of Dye.—There were forty-six patients with no retention of bromsulphalein before operation. The detailed findings in this group are presented in table 3. It will be noted that a postoperative increase in bilirubinemia occurred in twenty-seven cases (60 per cent) and retention of dye in nineteen cases (41 per cent).

Patients with Preoperative Retention of Dye.—There were fourteen patients in whom retention of dye (from 5 to 100 per cent) was present before operation. The detailed findings are presented in table 4. A postoperative increase in the bilirubin content of the blood occurred in eight cases (57 per cent); an increase in the degree of retention of dye in eight cases (57 per cent), and a decrease in the retention of dye in five cases (36 per cent).

Patients with No Preoperative Hyperbilirubinemia.—There were fifty-one patients in whom the concentration of serum bilirubin was within normal limits before operation. The detailed findings are presented in table 5. The concentration of serum bilirubin increased following operation in thirty-three cases (66 per cent), and the degree of retention of dye increased in twenty-three cases (45 per cent) and decreased in three cases (6 per cent).

Patients with Preoperative Hyperbilirubinemia.—There were nine patients with preoperative hyperbilirubinemia. The detailed findings are presented in table 6. A postoperative increase in the concentration of serum bilirubin occurred in two (22 per cent), and a decrease in seven (78 per cent); a postoperative increase in the degree of retention of dye occurred in four cases (44 per cent), and a decrease in two (22 per cent).

COMMENT

As was stated earlier, hyperbilirubinemia and retention of bromsulphalein eventually disappeared in every case in this series, although in some instances one or the other persisted for as long as four days. Retention of dye usually persisted longer than hyperbilirubinemia in cases in which both were present twenty-four hours after operation.

The question naturally arises as to why even temporary impairment of the excretory function of the liver should occur following cholecystectomy. The possible influence of anesthesia is obviously of importance. Chloroform was not employed for any patient in this group, nor was avertin, which, according to Bourne and Raginsky,[2] may cause increased retention of bromsulphalein in the presence of hepatic damage. There seems to be little doubt that ether has a distinct effect on certain hepatic functions. A moderate diminution in the glycogen content of the liver following ether anesthesia was reported by Evans, Tsai and Young [3] and by Macleod and Pearce.[4] A rise in venous blood sugar during and after the administration of ether has been demonstrated by a number of investigators, including Mekie and Miller,[5] Mackay,[6] Ross and Davis,[7]

2. Bourne, W., and Raginsky, B. B.: Effect of Avertin upon the Normal and Impaired Liver, Am. J. Surg. **14**:653, 1931.

3. Evans, C. L.; Tsai, C., and Young, F. G.: The Behavior of Liver Glycogen in Experimental Animals, J. Physiol. **73**:67, 1931.

4. Macleod, J. J. R., and Pearce, R. G.: Studies in Experimental Glycosuria: VI. The Distribution of Glycogen Over the Liver Under Varicus Conditions, Am. J. Physiol. **27**:341, 1911.

5. Mekie, E., and Miller, H.: Effects of Anesthesia, Operation and Certain Other Factors on Glycemia, Brit. M. J. **1**:244, 1929.

6. Mackay, R. L.: Atypical Case of Hyperglycemia in General Anesthesia, Brit. M. J. **1**:892, 1928.

7. Ross, E. L., and Davis, L. H.: The Rôle of the Pancreas in Hyperglycemia from Ether, Am. J. Physiol. **53**:391, 1920.

Mahler [8] and Cantarow and Gehret.[9] This ether hyperglycemia is generally attributed to increased hepatic glycogenolysis.

Although the importance of the hepatic glycogen content to the maintenance of hepatic function and to the capacity of the liver for resisting injury is well recognized, the metabolic functions of the liver, glycogenesis and glycogenolysis, at least, are more seriously affected by ether than are its excretory functions. In marked contrast to their observations following the administration of chloroform, Rosenthal and Bourne [10] noted only slight and transient retention of bromsulphalein following ether anesthesia for periods of from one-half to two hours. The average retention in the latter instance was 14 per cent (fifteen minute retention), normal values being invariably obtained within twenty-four hours. On the other hand, Rathery and Saison [11] reported degenerative hepatic lesions following prolonged ether anesthesia in animals, and in thirty-eight cases Chevrier [12] noted hyperbilirubinemia, which was greater in degree but much more transient than that following the administration of chloroform. Quénu, Duval and Brulé [13] also reported the presence of urobilinuria in several cases. However, the observations of the French investigators are not corroborated by those of the majority of workers in this field and are not in accord with our experimental and clinical findings. Ether appears to exert a distinct effect on the flow of bile, to which reference will be made later.

The work of Rosenthal and Bourne [10] indicated that nitrogen monoxide in the quantities administered to patients in this series produces no demonstrable impairment of hepatic function. Although the preoperative administration of morphine may cause transitory retention of bromsulphalein this effect, as demonstrated by Rosenthal and Bourne [10] and as observed by us, invariably disappears within from twelve to twenty-four hours. No such effect has been noted following anesthesia produced by infiltration of procaine hydrochloride or spinal anesthesia. It appears, therefore, that so far as direct hepatotoxic action

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8. Mahler, A.: Blood Cholesterol During Ether Anesthesia, J. Biol. Chem. **69**:653, 1926.

9. Cantarow, A., and Gehret, A. M.: Ether Hyperglycemia, with Especial Reference to Hepatic Disease, J. A. M. A. **96**:939 (March 21) 1931.

10. Rosenthal, S. M., and Bourne, W.: Effect of Anesthetics on Hepatic Function, J. A. M. A. **90**:377 (Feb. 4) 1928.

11. Rathery, F., and Saison, M.: Influence nocive de l'éther en inhalation sur le foie et le rein, Tribuna méd. **43**:245, 1910.

12. Chevrier, L.: Etudes sur la cholémie post-anesthésique et sur les moyens de la modifier, Bull. et mém. Soc. de chir. de Paris **45**:735, 1919.

13. Quénu, E.; Duval, P., and Brulé, M.: Etudes sur la cholémie, post-anesthésique et sur les moyens de la modifier, Bull. et mém. Soc. de chir. de Paris **45**: 833, 1919.

is concerned, anesthesia played a relatively unimportant part in the production of the observed postoperative changes in bilirubinemia and excretion of dye. This is further borne out by the fact that there was no correlation between the type or duration of anesthesia and either the incidence or the severity of the postoperative changes.

Several observers have described the effects of cholecystectomy on the flow of bile. The work of Rous and McMaster,[14] McMaster and Elman [15] and many others during the past thirteen years indicates that the chief demonstrable functions of the gallbladder are the concentration and storage of bile. By virtue of these functions the relatively large volume of bile which is being excreted continually by the liver is diminished (to one-sixth or one-eleventh its original volume), and the continuous flow from the liver is converted into an intermittent flow into the duodenum in accordance with physiologic demands for the presence of bile in the digestive mixture. One would expect removal of the gallbladder to result in well defined changes in the flow of bile. The influence of ether anesthesia in this connection cannot be disregarded. Mann [16] showed that the flow of bile was distinctly diminished in dogs during ether anesthesia, although no changes could be demonstrated in the liver. McMaster, Broun and Rous [17] confirmed this observation, noting in addition that the bile was highly concentrated and deeply pigmented, which would cast doubt on the probability of the existence of marked hepatic functional impairment, at least so far as the excretion of bile pigment is concerned. Diminution in, or at times complete cessation of, bile flow during operations on the bile passages under ether anesthesia has been noted, among others, by Nielson and Meyer,[18] Wertheimer [19] and Hooper and Whipple.[20]

As stated earlier, McMaster, Broun and Rous [17] found that during the first few days after cholecystectomy and intubation of the common duct the bile flow was almost invariably scanty, syrupy in consistency

14. Rous, P., and McMaster, P. D.: The Concentrating Activity of the Gallbladder, J. Exper. Med. **34**:47 (July) 1921.

15. McMaster, P. D., and Elman, R.: Studies on Urobilin: Physiology and Pathology, J. Exper. Med. **41**:513, 1925.

16. Mann, F. C.: Investigations of the Relation of Anesthesia to Hepatic Function, Anesth. & Analg. **4**:107, 1925.

17. McMaster, P. D.; Broun, G. O., and Rous, P.: Studies on the Total Bile: I, J. Exper. Med. **37**:395, 1923.

18. Nielson, N. M., and Meyer, K. F.: The Reaction and Physiology of the Hepatic Duct and Cystic Bile of Various Laboratory Animals, J. Infect. Dis. **28**: 510 (May-June) 1921.

19. Wertheimer, E.: Sur la circulation entéro-hépatique de la bile, Arch. Physiol. norm. et path. **4**:577, 1892.

20. Hooper, C. W., and Whipple, G. H.: Bile Pigment Metabolism: I. Bile Pigment Output and Diet Studies, Am. J. Physiol. **40**:332, 1916.

and deeply pigmented. Not until after from three to seven or more days did the volume of the flow reach the quantity yielded during the succeeding weeks. McMaster attributed this phenomenon largely to the effect of the operation on the liver, although the low intake of food may have been a contributory factor. By direct observation Puestow [21] found that cholecystectomy has a definite and constant effect on the flow of bile into the duodenum. Whereas with the gallbladder intact there is no flow into the intestine during fasting, in the cholecystectomized animal there is a constant flow under low pressure, the orifice of the common duct being almost always open. Furthermore, in the absence of the gallbladder, the stimulating influence of food on the flow of bile was found to be almost absent during the period before physiologic compensation was established. It is probable also that this abnormal, almost continuous flow of small quantities of bile into the duodenum further diminishes the stimulus to secretion of bile by the liver, which is normally supplied by reabsorption of relatively large quantities of bile acids periodically discharged into the duodenum.

Under normal conditions the quantity of bile pigment excreted by the liver in twenty-four hours is remarkably constant. The studies of Greene and Snell [22] indicated that the liver is normally able to secrete bile of a widely varying concentration of bilirubin (from 20 to 1,000 mg.). They stated that increased excretion of bilirubin in the bile is brought about primarily by an increase in the concentration of the pigment, although when excessive amounts are present there may be an additional increase in the volume of the output. Comparatively little is known regarding the factors which determine the elimination of bilirubin in the presence of hepatic disease. However, we have at hand experimental evidence which, with clinical observations, suggests that in the presence of functional impairment the liver, just like the kidney, loses its power of concentration, and, as in renal disease, the required quantity of solids can be excreted only by increasing the volume of fluid eliminated simultaneously. Choleresis in hepatic disease, therefore, may be regarded as an effort to compensate for diminution in the concentrating power of the liver, being analogous to the polyuria of early renal functional impairment in chronic glomerulonephritis. Under such circumstances any factor which tends to diminish the volume of bile would increase the tendency toward retention in the blood of those substances which can no longer be excreted in high concentration. Among these are bilirubin and perhaps bromsulphalein.

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21. Puestow, C. B.: The Discharge of Bile into the Duodenum: An Experimental Study, Arch. Surg. **23**:1013 (Dec.) 1931.

22. Greene, C. H., and Snell, A. M.: Studies in the Metabolism of the Bile: II. The Sequence of Changes in the Blood and Bile Following the Intravenous Injection of Bile or Its Constituents, J. Biol. Chem. **78**:691, 1928.

In the light of previous studies reported by one of us,[23] as well as by Judd,[24] Graham and his associates,[25] Tietze and Winkler[26] and many others, it is probable that some diminution in the hepatic functional reserve, if not actual organic hepatic disease, is present in a large proportion of persons with chronic disease of the biliary tract. When in the presence of diminution in the concentrating ability of the liver cholecystectomy is performed, increased retention of bilirubin and bromsulphalein may conceivably result from the sudden consequent diminution in the volume of the flow of bile.

Naturally, in addition to the nature and duration of the anesthesia, such factors as the preoperative state of hepatic function and the extent of operative manipulation are of importance in determining the degree of postoperative hepatic functional impairment. However, analysis of the data obtained in the present series of cases reveals no consistent

TABLE 7.—*Summary of Data for Patients with Patent Cystic Duct*

	Retention of Dye		Serum Bilirubin	
Cases	Increased	Decreased	Increased	Decreased
34	25 (73%)	0	27 (79%)	4 (12%)

TABLE 8.—*Summary of Data for Patients with Nonpatent Cystic Duct*

	Retention of Dye		Serum Bilirubin	
Cases	Increased	Decreased	Increased	Decreased
26	2 (17%)	5 (19%)	8 (31%)	13 (50%)

relationship between these factors and the postoperative functional changes. The factor which appeared to be of significance in this connection was that of obstruction of the cystic duct, as demonstrated by cholecystography or at operation. The detailed data bearing on this point are presented in tables 7 and 8. It will be noted that cholecystec-

23. Cantarow, A.: The van den Bergh Reaction and the Bromsulphalein Test in the Estimation of Hepatic Functional Impairment, Am. J. M. Sc. **184**:228, 1932; footnote 1.

24. Judd, E. S.: Relation of the Liver and the Pancreas to Infection of the Gallbladder, J. A. M. A. **77**:197 (July 16) 1921. Judd, E. S.; Nickel, A. C., and Wellbrock, W. L. A.: The Association of the Liver in Disease of the Biliary Tract, Surg., Gynec. & Obst. **54**:13, 1932.

25. Graham, E. A.: Hepatitis; a Constant Accompaniment of Cholecystitis, Surg., Gynec. & Obst. **26**:521, 1918. Peterman, M. G.; Priest, W. S., Jr., and Graham, E. A.: Association of Hepatitis with Experimental Cholecystitis and Its Bearing on the Pathogenesis of Cholecystitis in the Human, Arch. Surg. **2**:92 (Jan.) 1921.

26. Tietze, A., and Winkler, K.: Die Beteiligung des Leberparenchyms an der Gallensteinkrankheit, Arch. f. klin. Chir. **129**:1, 1924.

tomy was followed by an increase in the degree of retention of dye in twenty-five (73 per cent) of the thirty-four patients in whom the cystic duct was patent, as compared with two (17 per cent) of the twenty-six patients in whom the cystic duct was not patent. Increased bilirubinemia was observed in 79 per cent of the former group as compared with 31 per cent of the latter.

The probable explanation for this difference appears rather obvious. In persons with obstruction of the cystic duct, the biliary passages had been completely deprived of the functional activity of the gallbladder for some time prior to its removal; compensatory changes had occurred, as described by Puestow,[21] and cholecystectomy resulted in practically no further disturbance in the flow of bile. In patients with a patent cystic duct, the gallbladder, although not functioning normally, nevertheless carried a variable portion of the burden which, following its removal, was suddenly thrown on the hepatic and common ducts. This resulted in changes qualitatively if not quantitatively comparable to those which follow experimental cholecystectomy, as reviewed earlier.

SUMMARY

Determinations of serum bilirubin and retention of bromsulphalein were made before and after cholecystectomy in sixty patients with cholecystitis without obstruction of the common bile duct.

A temporary increase in serum bilirubin occurred in twenty-six (63.4 per cent) of forty-one patients with apparently normal preoperative hepatic function. Postoperative retention of dye was noted in sixteen (39 per cent) patients in this group.

Increased bilirubinemia occurred in nine (47.3 per cent) and increased retention of dye in eleven (57.9 per cent) of nineteen patients who showed some degree of hyperbilirubinemia or of retention of dye before operation.

This temporary postoperative impairment of hepatic excretory function bore no constant relation to the nature or duration of anesthesia or to the preoperative state of hepatic function in this group of patients. It is believed to be dependent probably on the decrease in the volume of the flow of bile which follows cholecystectomy and which interferes with the mechanism whereby a damaged liver compensates for impairment in its ability to concentrate certain solid constituents of the bile.

Patency or occlusion of the cystic duct appeared to be of significance in determining the occurrence of these postoperative functional abnormalities. Increased retention of dye occurred in 73 per cent and increased bilirubinemia in 79 per cent of the patients with patent cystic ducts, whereas the corresponding figures for the group with obstruction of the cystic duct were 17 and 31 per cent.

EFFECT OF JEJUNAL FEEDING ON GASTRIC ACIDITY

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In recent years jejunal feeding has been recommended for the treatment of complicated peptic ulcer. Occasionally at operation for ulcer the inflammatory reaction is found to be so intense as to make any extensive surgical procedure unsafe. Some patients have undergone jejunostomy as a palliative measure to maintain them until a more extensive operation could be performed and under such management have improved clinically. Another method of treatment has been to pass a long catheter through the nose or mouth down to the jejunum and to feed the patient through the tube for a period of from four to six weeks. Patients who had not improved with other forms of treatment were said to have improved under this management. Since the acid secretion of the stomach is so intimately concerned with the treatment of peptic ulcer, any method of lowering this secretion would be of some value in the treatment of ulcer. Jejunal feeding is said to lower the acidity of the gastric content. Accordingly, the present experimental study was undertaken to see what effect feeding through a jejunal fistula would have on the reaction of the gastric content.

There are three stimuli which can cause the gastric mucosa to secrete: (1) the sight, smell or taste of food, (2) the presence of certain foods in the stomach and (3) the presence of certain food substances in the intestine. It is with the third mechanism that the research reported here was primarily concerned.

Pavlov[1] noted an intestinal phase of gastric secretion. He found that the introduction of food substances into the duodenum was followed by secretion of gastric juice. Following his observation a series of reports was published in which was described the stimulating effect on gastric secretion of each of a large variety of food substances when introduced into the intestine. Outstanding among these investigations were those reported by Gross,[2] Ivy and Whitlow,[3] Chittenden, Mendel and

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1. Pavlov, I. P.: The Work of the Digestive Glands, ed. 2, London, Charles Griffin and Company, 1910.

2. Gross, W.: Beitrag zur Kenntnis der Sekretionsbedingungen des Magens nach Versuchen am Hund, Arch. f. Verdauungskr. **12**:507, 1906.

3. Ivy, A. C., and Whitlow, J. E.: The Gastrin Theory Put to Physiological Test, Am. J. Physiol. **60**:578 (May) 1922.

Jackson,[4] Edkins and Tweedy [5] and Kauders and Porges.[6] Many of the results reported were contradictory, but on the whole it was generally conceded that gastric secretion was stimulated when food was introduced into the duodenum. Ivy and his co-workers [7] attempted to obtain more accurate results by carefully controlled experiments, and they found that some foods when introduced into the intestine stimulated more gastric secretion than did others. Einhorn [8] applied this knowledge clinically and treated patients who had peptic ulcer by feeding them through a tube introduced into the duodenum; he reported good results. Friedenwald and Wiest [9] also reported cases in which similar treatment was employed. Levy [10] performed a fractional analysis of the gastric content of patients who were receiving duodenal alimentation and found a definite rise in gastric acidity in spite of the clinical improvement. Garbat [11] obtained similar results and studied the problem in more detail, establishing the fact that acid gastric secretion was stimulated by the duodenal feeding of patients with peptic ulcer.

In an attempt to prevent the stimulation of gastric secretion, Bockus [12] fed patients who had ulcer through a tube placed in the jejunum, and found that after this treatment, when the ulcer was healing, gastric acidity was reduced. Henning [13] studied the problem in detail, introducing many food substances into the jejunum to determine

4. Chittenden, R. H.; Mendel, L. B., and Jackson, H. C.: A Further Study on the Influence of Alcohol and Alcoholic Drinks upon Digestion, with Special Reference to Secretion, Am. J. Physiol. **1**:164 (March) 1898.

5. Edkins, J. S., and Tweedy, M.: The Natural Channels of Absorption Evoking the Chemical Mechanism of Gastric Secretion, J. Physiol. **38**:263 (March 22) 1909.

6. Kauders, F., and Porges, O.: Der Einfluss des Duodenalinhaltes auf die Magensekretion, Wien. klin. Wchnschr. **35**:838 (Oct. 26) 1922.

7. Ivy, A. C.; Lim, R. K. S., and McCarthy, J. E.: II. The Intestinal Phase of Gastric Secretion, Quart. J. Exper. Physiol. **15**:55, 1925. Ivy, A. C., and McIlvain, G. B.: Excitation of Gastric Secretion by Application of Substances to the Duodenal and Jejunal Mucosa, Am. J. Physiol. **67**:124 (Dec.) 1923.

8. Einhorn, M.: A Case of Perforation of the Duodenum Treated Successfully by Duodenal (Jejunal) Alimentation, M. Rec. **94**:927 (Nov. 30) 1918; Duodenal Alimentation, ibid. **78**:92 (July 16) 1910; Results of Duodenal Alimentation in Peptic Ulcers, ibid. **96**:95 (July 19) 1919.

9. Friedenwald, J., and Wiest, P. F.: Some Observations on Duodenal Alimentation, New York M. J. **117**:655 (June 6) 1923.

10. Levy, M. D.: The Fractional Estimation of the Gastric Contents During Duodenal Alimentation, Texas State J. Med. **16**:483 (March) 1921.

11. Garbat, A. L.: Gastric Secretion in Response to Duodenal Feeding, Arch. Int. Med. **32**:771 (Nov.) 1923.

12. Bockus, H. L.: Jejunal Alimentation in Treatment of Peptic Ulcer, J. A. M. A. **82**:351 (Feb. 2) 1924.

13. Henning, N.: Untersuchungen über die duodenale und jejunale Ernährung. I. Einfluss der duodenalen und jejunalen Ernährung auf die Nüchternsekretion, Arch. f. Verdauungskr. **41**:321 (Dec.) 1927.

their effects on gastric secretion, and found that the food substances which stimulated gastric secretion when given by duodenum did not do so when given by jejunum. Later, with Morawitz,[14] he reported beneficial effects of jejunal feeding through a long catheter in cases of peptic ulcer. Rehder,[15] Gutzeit[16] and Mouzon[17] obtained clinical improvement in cases of ulcer by means of jejunal feeding.

Jejunostomy for jejunal feeding in cases of complicated peptic ulcer has been recommended by many authors. Outstanding among them were Heyd,[18] Walker[19] and Laméris.[20] They found that inoperable ulcers often healed completely, or at least to such an extent that radical operation at a subsequent date could be performed with lessened risk. Scott and Ivy[21] found that most diets used in jejunal feeding were successful if used only for a few weeks. After this time most foods proved to be irritating to the small intestine. Accordingly, they prepared a diet which lowered gastric secretion when fed by jejunum and which could be administered over long periods to dogs without any evidence of irritation. Mensing[22] gave this diet through a jejunostomy tube to his patients who had ulcer and obtained good clinical results.

METHOD OF PROCEDURE

In this study an attempt was made to determine what effect jejunal feeding would have on the secretory activity of the stomach. Gastric and jejunal fistulas were made in dogs, the intestinal loop type of fistula as described by Mann and Bollman being used.[23] The jejunal fistulas were placed approximately from 10 to 20 cm. from the ligament of Treitz. All of the operations were performed with the animals under ether anesthesia, and a sterile technic was employed.

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14. Morawitz, P., and Henning, N.: Ueber jejunale Ernährung, Klin. Wchnschr. **8**:681 (April 9) 1929.

15. Rehder, R.: Ulkusbehandlung mit der jejunalen Ernährung im Privathaus, Med. Welt **3**:1728 (Nov. 30) 1929.

16. Gutzeit, K.: Ueber die Beeinflussung der Magenreiz- und Nüchternsekretion durch Dünndarmverweilsonden sowie durch duodenale und jejunal Nahrungszufuhr, Ztschr. f. d. ges. exper. Med. **73**:48, 1930; Ueber die therapeutischen Erfolge der duodenalen bzw. jejunalen Ernährung bei Magenkranken, München. med. Wchnschr. **77**:446 (March 14) 1930.

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19. Walker, I. J.: Jejunostomy, Boston M. & S. J. **186**:108 (Jan. 26) 1922.

20. Laméris, H. J.: Zur Behandlung des Magengeschwürs, Deutsche Ztschr. f. Chir. **189**:1, 1924.

21. Scott, H. G., and Ivy, A. C.: Jejunal Alimentation: An Experimental Study in Dogs, Ann. Surg. **93**:1197 (June) 1931.

22. Mensing, E. H.: Treatment of Certain Cases of Duodenal Ulcer by Jejunostomy, Am. J. Surg. **15**:105 (Jan.) 1932.

23. Mann, F. C., and Bollman, J. L.: A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract, Ann. Surg. **93**:794 (March) 1931.

The routine established in making observations was as follows:

1. Each dog was given a mixture of milk and syrup (10 per cent syrup in the whole milk) by mouth three times daily in sufficient amount to supply the necessary fluid and caloric requirement. Specimens of gastric content were withdrawn every hour for a period of eight hours. The p_H, free acidity and total acidity were determined. The p_H value of the gastric juice was obtained by the quinhydrone method, and the titrations for the acid values were made with a tenth-normal solution of sodium hydroxide, 1 per cent phenolphthalein and a 0.5 per cent alcoholic solution of dimethyl-amino-azobenzene being used as indicators. A rough measure of the amount of secretion was also noted. The mixture of milk and syrup was selected because it was always available, being used as a routine for postoperative feeding, and because the dogs had maintained their weight and general condition when fed this mixture over a period of several months. When constant readings were obtained, the mixture was fed by jejunum three times daily, and following this it was again given by mouth as a check on the first set of readings. The dogs were made to fast for at least eighteen hours before each set of experiments.

2. The dogs were then given five feedings daily by mouth, then by jejunum, and then again by mouth, as before. The total number of cubic centimeters of milk and syrup used was the same for each dog per day.

3. In order to determine whether or not an intestinal fistula connected with the stomach would have any effect on the gastric p_H and acidity, three dogs were used which had no gastric fistula but only an intestinal fistula, the specimens of gastric juice being withdrawn by means of a stomach tube. Two dogs which had only a duodenal fistula were used for a study of the p_H of the duodenal content following feeding of the same mixture of milk and syrup three and five times daily.

4. In order to determine whether or not some of the secretion was due to psychic stimulation, although great care was exercised in all experiments to prevent this, two dogs were given sodium amytal by jejunum in doses sufficient to produce sleep, and determinations were made as before.

5. Some of the simpler food substances were tested to determine whether or not a nonstimulating food could be found. The dogs fasted, then the individual food substances were given by jejunum, gastric juice was withdrawn at intervals of half an hour for from three to four hours, and the usual determinations were made. At least two dogs were used for each food substance tested, and readings were obtained for at least two days. The following substances were used: casein, 2 Gm. per kilogram; butter, 1 Gm. per kilogram; cream, 3 cc. per kilogram; cottonseed oil, 3 cc. per kilogram; sucrose, 2 Gm. per kilogram; dextrose, 2 Gm. per kilogram; flour, 2 Gm. per kilogram; eggs, approximately one per 10 kilograms; peptone, 2 Gm. per kilogram; Liebig's meat extract, 1 Gm. per kilogram; glycine, 1 Gm. per kilogram, and the special diet devised by Ivy.

RESULTS

Amount of Secretion.—In general, more secretion was withdrawn from the stomach when the milk was fed by jejunum than when it was fed by mouth. In the two dogs which had only a jejunal fistula and from which the gastric content was withdrawn by stomach tube, there was no appreciable difference in the amount of secretion obtained whether they were fed by mouth or by jejunum, probably because the

stomach tube was less efficient than the catheter inserted through a fistula in withdrawing the gastric content. Furthermore, there was a greater amount of secretion when five feedings were given daily than when only three feedings were given, even though the total number of cubic centimeters of the milk mixture was the same in each case.

Hydrogen Ion Concentration of the Gastric Content.—Lower values for the p_H of the gastric content were obtained with jejunal feedings than with oral feedings, and these values were appreciably lower when five feedings were given daily than when three feedings were given daily.

Free Acidity of the Gastric Content.—There was little or no free acid in the gastric content with oral feeding, but a moderate amount was present with jejunal feeding. Occasionally the free acidity reached a high level. Moreover, the free acidity reached a higher level when five feedings were given daily than when three feedings were given daily.

Average Maximal Acidity of the Gastric Content Following the Jejunal Feeding of Various Food Substances

Food Substance Used	p_H	Free Acid*	Total Acid*
Sucrose	5.91	2.5	13
Peptone	5.14	2.5	25
Butter	4.68	4.0	25
Flour	4.77	5.0	20
Eggs	5.35	5.0	22
Dextrose	5.31	7.5	22
Cream	3.61	8.5	42
Liebig's extract	4.38	9.0	41
Glycine	3.98	16.0	42
Cottonseed oil	3.33	16.0	43
Casein	3.81	16.0	57

* The method of obtaining the values is given in the text.

Total Acidity of the Gastric Content.—The total acidity was practically the same with oral as with jejunal feeding when three feedings a day were given, but with five feedings a day the value was higher with jejunal feeding than with oral feeding.

Hydrogen Ion Concentration of the Duodenal Content.—In the two dogs with duodenal fistulas in which duodenal specimens were withdrawn, it was noted that the duodenal p_H was higher with jejunal feeding than with oral feeding and that the p_H was slightly lower with five feedings than with three feedings daily.

Psychic Secretion of Gastric Juice.—It was thought that the high acidity of the juice obtained with jejunal feeding might perhaps be due to psychic secretion, since these dogs would go for periods of four or five days at a time without food by mouth. In order to decide this point, two of the dogs were given sodium amytal by jejunum. It was found that 18 mg. per kilogram of body weight would make the dogs sleep soundly. With the dogs thus anesthetized, the secretion was just as great and the juice was just as acid as when they were awake.

Effect of Different Food Substances.—The feeding by jejunum of each of the food substances, including Ivy's preparation, was followed by some secretion of gastric juice. The effect of the various foods on gastric secretion differed markedly (table).

COMMENT

The results obtained from this investigation indicate that most foods when placed in the jejunum will stimulate gastric secretion. In these experiments it was found that during fasting the stomach secreted a few centimeters of thick, white mucus, with a p_H of about 7, which did not contain any free acid and which contained only a little combined acid. This finding was considered to indicate that the gastric mucosa was not secreting. Stimulation of gastric secretion was considered to have occurred when the specimens began to contain free acid and the p_H decreased.

All the foods used in jejunal feeding appeared to stimulate gastric secretion, but some foods produced greater gastric acidity than others. Thus, feeding sucrose, peptone, butter, flour and eggs was followed by the production of only a small amount of acidity, while feeding cream, Liebig's meat extract, cottonseed oil, casein and glycine was followed by the production of relatively high acidity.

SUMMARY

In this study an attempt was made to determine the effect of jejunal feeding on gastric acidity and secretion. Dogs with gastric and jejunal fistulas were used. It was found that a mixture of milk and syrup when fed by jejunum stimulated gastric secretion and increased the acidity of the gastric content. Greater stimulation occurred when the mixture was fed five times daily than when it was fed three times daily, even though the total number of cubic centimeters of the mixture was the same in each instance. The gastric content was more acid and had a lower p_H when the mixture was fed by jejunum than when it was fed by mouth. The results were the same whether the specimens were obtained through a gastric (intestinal loop type) fistula, by means of a catheter and syringe or through a stomach tube from a dog with no fistula. Psychic secretion was not a factor in these experiments, as was shown by the results obtained when the dogs were under the influence of sodium amytal. A number of simpler food substances were tested, and were found to stimulate gastric secretion in the following order, from least to most: sucrose, peptone, butter, flour, eggs, dextrose, cream, Liebig's extract, glycine, cottonseed oil and casein. The duodenal content was found to be slightly more alkaline following jejunal feeding than following oral feeding.

EFFECT OF ENEMAS ON INTESTINAL MOTILITY

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Various types of enema are recommended for the relief of postoperative abdominal distention. The beneficial action of these enemas has frequently been attributed to a reflex stimulation of the small intestine, but proof of such action has not been found in the literature. That the rate of expulsion of enemas in a dog with an obstruction is similar to that in a normal dog has been shown by Wangensteen and Goehl.[1]

EXPERIMENTAL METHODS

Kymographic tracings of the ileum and jejunum of normal dogs were taken before, during and after the administration of various enemas. The tracings of the ileum were taken through ileostomy openings which were made just before the experiment was begun. The tracings of the jejunum were made through recently prepared Thiry-Vella loops.[2]

Enemas of tap water, physiologic solution of sodium chloride, hypertonic solution of sodium chloride, soap-suds and a mixture of magnesium sulphate, oxgall, glycerin and water were given. The effect of distending the colon with air was also studied. From 100 to 400 cc. of liquid were used in each enema.

RESULTS

Enemas of tap water, soap suds, physiologic solution of sodium chloride and a mixture of magnesium sulphate, oxgall, glycerin and water and injections of air did not show any effect on the motility of the small intestine. The only change from the normal tracings occurred when the enemas were being expelled, at which time strong contractions of the rectus muscles compressed the intestine.

Enemas of hypertonic solution of sodium chloride in concentrations of 2, 10 and 20 per cent and saturated solution (about 36 per cent) regularly increased peristalsis in from five to ten minutes. The strong solutions produced the greatest effect. The action of the hypertonic solution of sodium chloride may have been due to the

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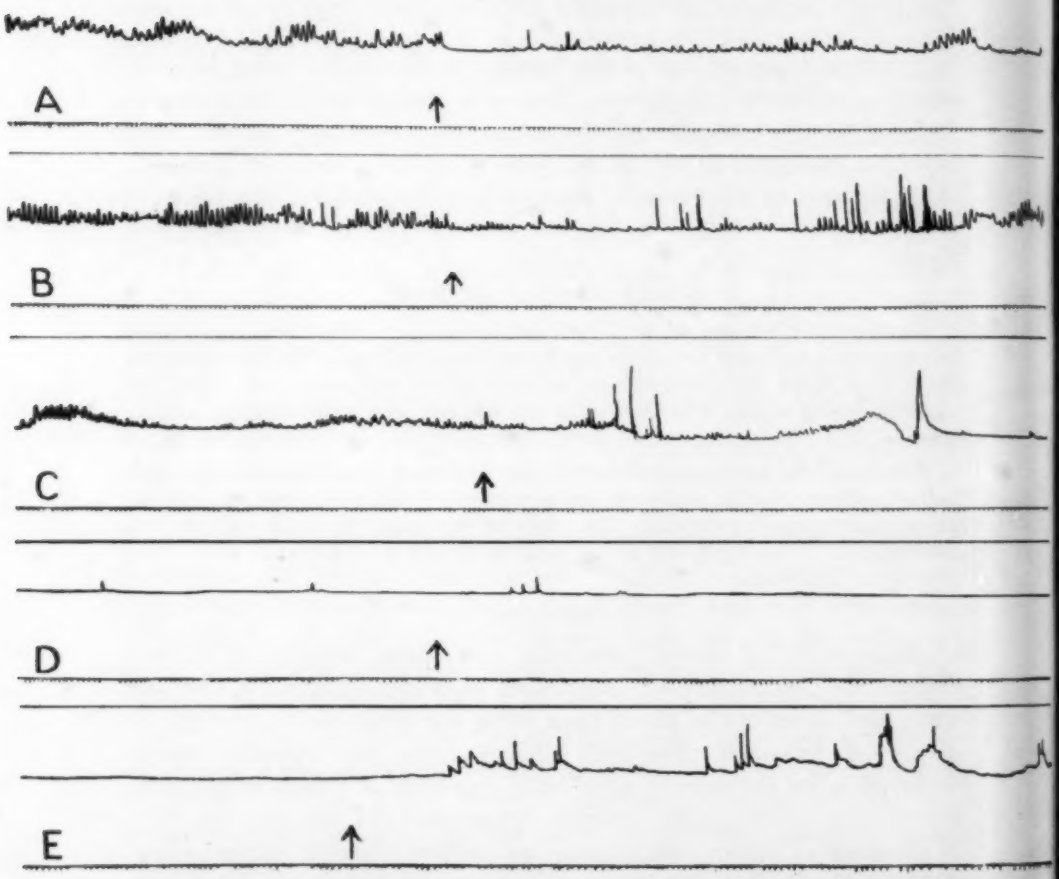
1. Wangensteen, O. W., and Goehl, R. O.: Evaluation of the Expulsion of Enemas as a Criterion of Intestinal Obstruction, Arch. Int. Med. **46**:669 (Oct.) 1930.

2. Orr, T. G.: The Action of Sodium Chloride upon the Small Intestine, Ann. Surg. **94**:732, 1931.

absorption of salt into the blood stream from the colon, since a study of the blood showed an increase in the chloride content in from one to three hours after the injection. The stronger solutions of salt produced severe proctitis.

SUMMARY

The action of simple and irritant enemas on the motility of the ileum and jejunum were studied experimentally by recording the con-



Tracings of the ileum and jejunum before and after the injection of various types of enema. In each instance the portion of the tracing to the left of the arrow is of the normal intestine before the injection and the portion to the right is of the intestine after the injection of the specified enema. *A* shows the effect on the ileum of the injection of an enema of 200 cc. of air by rectum; *B*, the effect on the ileum of an enema of 200 cc. of tap water; *C*, the effect on the ileum of an enema of 200 cc. of magnesium sulphate, glycerin, oxgall and water; *D*, the effect on the jejunum of an enema of 400 cc. of soap-suds, and *E*, the effect on the jejunum of an enema of 200 cc. of a 10 per cent solution of sodium chloride. The sharp contractions noted in the first three tracings were caused by the muscular effort to expel the enema. The enema of hypertonic solution of sodium chloride caused an increase in intestinal tone and peristalsis.

tractions of the intestine by means of a rubber balloon before, during and after the enemas were given.

No increase of motility of either the jejunum or the ileum was noted except with hypertonic solutions of sodium chloride. Clinical experiments have not been made with enemas of hypertonic solutions of sodium chloride.

The suggestion that the enemas commonly used are active in relieving abdominal distention by reflex action on the small intestine was not supported by this study. Enemas as usually given should be depended on only to aid in emptying the colon.

A REVIEW OF UROLOGIC SURGERY

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Hydronephrosis.—Lichtenberg [1] described a pathologicophysiologic principle which aids in differentiating the dynamic and the mechanical form of renal obstruction and in selecting the method of surgical treatment with more assurance and success. Testing the response of the pelvic and ureteral musculature to electrical stimulation at the time of operation will reveal whether conservative surgical therapy is indicated. Lichtenberg stated that a pathologicophysiologic point of view of renal obstruction might open up new methods in treatment in those cases in which surgical intervention is not necessary.

Pelliccia [2] discussed the etiology of intermittent hydronephrosis in 2 cases in which he recently had occasion to operate. Defining intermittent hydronephrosis as the phenomenon of successive attacks of acute and sudden retention of urine in the renal pelvis, which are followed within a few hours or during the course of a day by its complete outflow, with no disturbances between attacks, he maintained that the symptoms in such cases are distinctly different from those of common hydronephrosis, as are also the etiologic factors. The particular variations of diuresis are characteristic; urine is scanty during the attack and abundant at its end, and although hematuria is sometimes present the urine is otherwise normal.

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1. Lichtenberg, A.V.: Die pathologische Physiologie der renalen Verstopfung, und die sich daraus ergebenden konservativ-chirurgischen Massnahmen, Acta chir. Scandinav. **74**:283, 1934.

2. Pelliccia, Gilberto: Due case di idronefrosi intermittenti, Arch. ital. di urol. **11**:246 (April) 1934.

The same causes that produce hydronephrosis in general may give rise to intermittent hydronephrosis, but some of these causes are observed with greater frequency in cases of the latter condition, and it is with these that the author is concerned. Chief among them are malformations, and these may be either congenital or acquired. Among the former are anomalies of the renal pelvis, stenosis of the ureter, valvular folds, anomalous blood vessels and lesions of the nerves. Among acquired malformations are renal ptosis, strictures of the ureter and renal lithiasis.

In the author's first case the patient was a woman 24 years of age, and the intermittent attacks of hydronephrosis dated from the age of 7 years, when they had been mistaken for appendical colic. This led to fruitless appendectomy when the patient was 13 years of age. A sound introduced into the ureter by Pelliccia revealed an S-shaped structure, demonstrating that the ureter deviated greatly from its normal position, possibly because of the descent of the hydronephrotic sac, which reached almost down to the iliac crest. On the basis of the roentgenographic and pathologico-anatomic observations, which revealed that the ureter deviated laterally to a considerable extent on leaving the renal pelvis and that at the start it was markedly contracted, Pelliccia accepts the hypothesis that this stenosis and deviation constituted a congenital malformation which represented the first obstacle to the urinary outflow and that in the factors bringing about polyuria, which may be the result of any one of several causes—stenosis of the ureter or bagpipe shape of the renal pelvis—there was stasis with consequent increase of intrapyelic pressure. This may result in a false valve on the ureteral ostium or may provoke a spasm of the ureter until hypertension reaches a point capable of arresting the secretion of urine and of causing paresis of the ureter, with relaxation of its walls, overcoming the spasmodic closure and permitting the outflow of the urine.

In the second case the sound introduced into the ureter met an obstruction at a point 10 cm. from its orifice into the bladder, beyond which it was markedly contracted. That this stenosis was of congenital origin is confirmed by the abnormality of the vesical orifice. It is logical to assume that the incapacity of the abnormally contracted ureter for permitting the outflow of the increased volume of urine under conditions of increased diuresis to which the patient was subject resulted in stagnation, with distention of the sac. It may be that at such times reflex spasms of the ureter also occurred, which would explain the complete arrest of the outflow sometimes observed. When the increased pressure in the pelvis of the kidney was sufficient to arrest diuresis and the spasm of the ureter was relaxed, spontaneous outflow of the collection occurred.

Calculi.—Nash [3] stated that most cases of calculous pyonephrosis occur among young women who marry at an early age and rapidly go through multiple pregnancies. There may be urinary diathesis which predisposes such women to infection and to the formation of a stone in the kidneys, a condition analogous to that of women with biliary diathesis in whom the disease of the gallbladder has its origin at the time of the first pregnancy. The treatment of the acute and of the chronic type was considered. For the latter it was suggested that nephrotomy be done first, to be followed by secondary transperitoneal nephrectomy, because the abdominal approach enables one to avoid hemorrhage and other complications incident to lumbar nephrectomy.

Twinem [4] reported that bilateral involvement is present in about 13 per cent of cases of renal stone. Bilateral lithiasis is usually preceded by a bilateral infection. A bilateral operation should be done only in cases in which the stones can be removed easily, in which the patient is young and in which only slight or no infection is present. Usually the better kidney should be operated on first. Certain exceptions were mentioned. The surgical indications in cases of various types of bilateral stones were discussed. The patient requires the most meticulous care if the best results are to be obtained.

Tumor.—Ceccarelli [5] reported a case of an unusual variety of renal adenoma of complex structure, which is not easy to interpret or to classify and a study of which raises important questions with reference to the histogenesis of an entire series of renal tumors of similar structure, variously classified now as hypernephroid tumors and angioepitheliomas.

At operation on a woman who had suffered from renal colic on the left side a spheroid tumor the size of a mandarin orange was found; the growth was half embedded in the parenchyma and reached the renal pelvis. It was wine red and of a soft and almost fluctuating consistency and was surrounded by a smooth fibrous capsule. From this capsule a great number of trabeculae could be seen entering the interior of the tumor, dividing it into many compartments; coursing through the trabeculae were numerous small blood vessels or dilated capillaries which frequently constituted the entire skeleton of the septum. In some instances epithelial cells rest directly on these. The tumor was thus seen to be an adenomatous new growth in which the vascular

3. Nash, I. E.: Calculous Pyonephrosis: Clinical Study with Especial Reference to Etiology and Treatment; Review of Its Literature; Report of 6 Cases, Am. J. Surg. **24**:110 (April) 1934.

4. Twinem, F. P.: Surgical Management of Bilateral Nephrolithiasis, Am. J. Surg. **24**:124 (April) 1934.

5. Ceccarelli, G.: Su di una forma rara di adenoma renale, Arch. ital. di urol. **11**:223 (April) 1934.

element was so strongly developed that it had to be considered an integral part of the tumor. This led the author to inquire whether it might not be possible to classify it among certain varieties of hypernephroid tumors, in which the characteristic vascular development is particularly accentuated and in which there is an intimate relation between blood vessels and epithelial elements.

It is rather worthy of remark that despite this abundance of vessels there had been no macroscopic hematuria, although microscopic hematuria had occurred shortly before operation. The compartments were in some places filled with well conserved blood and in other places chiefly, or almost exclusively, with an amorphous homogeneous substance resembling colloid. Many of the cavities were lined with cylindric or cuboid epithelium or even by flattened elements of endothelial type, and in the lumens of some of the cavities papillary formations were seen protruding.

Ceccarelli, after reviewing the literature, in which considerable controversy is found with reference to the interpretation of similar new growths, concluded that his tumor must be regarded as a papilliferous adenoma, characterized by an unusually abundant vascular development and arising from embryonal rests that consist of epithelial cells and blood vessels of the kidney, which had remained shut off or deviated from the normal. In his opinion it is possible to interpret in this way a considerable number of new growths in the kidney, which are called by different names and are classified sometimes as hypernephroid tumors and sometimes as angio-epitheliomas; all, however, are characterized by the phenomena of blood vessels and epithelial cells growing together in intimate association. A bibliography of twelve references accompanies the article.

MacKenzie [6] stated that it is estimated that on an average the pelvic tumors comprise about from 5 to 7 per cent of all renal growths. Papillary growths represent about from 70 to 80 per cent of all tumors of the renal pelvis. Of these, from 60 to 70 per cent are benign and from 30 to 40 per cent are malignant. Several of them are on the borderline. The papillary growths of the renal pelvis are similar to the papillary growths of the bladder. They appear alike, they have the same characteristic property of forming transplants, and they simulate each other in their low grade malignancy. The simple papillomas are usually multiple and appear as villous or wartlike growths. Occasionally the growth has an extensive distribution and may involve the ureter and the bladder and even the ureter on the opposite side. Often there is one large growth with several smaller

6. MacKenzie, D. W.: Papillary Growths of the Renal Pelvis, Canad. M. A. J. **30**:509 (May) 1934.

ones surrounding it. Frequently the growths are associated with salty incrustations and even with definite calculi. The papillomas are all very vascular and bleed easily. This accounts for the marked hematuria that is usually the outstanding symptom in the disease. The growths are benign, but have a tendency, like the simple papillomas of the bladder, to become malignant. They do not metastasize but possess the quality of producing transplants along the ureter and in the bladder. The malignant papillomas are also wartlike or cauliflower-like in character but appear more compact and usually involve a greater area than the simple papillomas. At times the entire kidney is replaced by a growth. The villous processes are not as long or branching and often show areas of ulceration. Here, too, the growth may extend downward to involve the ureter and the bladder. In the early stages there is definite evidence of involvement of the submucosa, and later the renal parenchyma is encroached on. In most advanced cases there is distention of the renal pelvis and multiple cysts are present in the cortex of the kidneys. These tumors are also extremely vascular and bleed easily. Microscopically the essential tumor cells are found to have invaded the base of the growth and the submucosa. In some growths there are areas showing benign and malignant cells side by side, suggesting a transformation from a benign to a malignant state.

Carcinoma.—Gilbert and MacMillan [7] stated that primary squamous cell tumors of the renal pelvis are relatively rare, as approximately 57 cases have been previously reported. Thirty-one were in males and 26 were in females. The tumor occurred 26 times on the left side and 26 times on the right side, while in 5 cases the side involved was not stated. Pyuria was noted 39 times. This was consistently present in the cases coexisting with calculi and leukoplakia. This combination of infection and calculi led to the diagnosis of calculous pyonephrosis in most cases. Thirty of the 57 cases, or 52 per cent of squamous cell tumors of the pelvis of the kidney, were associated with calculi. These reports showed that calculi varied greatly in number, size and chemical structure. Multiple calculi were not unusual, and the calculi were frequently large. The growth in 31 cases was classified as squamous cell carcinoma, in 11 as epithelioma, in 9 as pavement cell epithelioma, in 3 as epidermoid carcinoma and in 1 case as scirrhous carcinoma, epithelioma carcinoid and "flat carcinomatous ulcer." Twenty-four cases, or 42 per cent of this series, were observed at necropsy. In other cases exploratory operation proved the presence of metastasis. Clinical examination alone often revealed the presence of widespread disease, as in Hartmann's case. Direct extension from the renal artery to the

7. Gilbert, J. B., and MacMillan, S. F.: Cancer of the Kidney, Ann. Surg. **100**:429 (Sept.) 1934.

vena cava occurred 5 times, and to the local lymph nodes, 9 times. Metastasis to bones was noted 8 times; the adjacent vertebrae were involved 5 times, and the seventh rib, the greater trochanter of the femur and the lower end of the femur were each involved once. Only early surgical removal of the carcinoma can save these patients. It is generally agreed that the diagnosis is made late in the course of the disease, when the kidney is fixed or when metastasis has already taken place. In several instances, nephrectomy for stone was carried out and the presence of tumor was not suspected. In other cases nephrectomy was done for drainage when the tumor was inoperable. In 18 cases no operative procedure was done. Operative procedures were carried out as follows: exploratory operation, 7 times; nephrotomy, 6 times, and nephrectomy, 36 times. In 15 cases of this series the length of life and the cause of death were not stated. Eight patients are reported to have died; 6 patients are reported to have had recurrence after operation, which caused death in between six months and one year; 26 patients died in the first six months after operation. Gilbert and MacMillan said that there were no five year cures in this series. The fact that these tumors are generally of a high degree of malignancy and that the clinical diagnosis is made late combine to make this disease uniformly fatal.

Keen [8] called attention to the similarity of the roentgenographic appearance of malignant and that of tuberculous (renal) calcification. Thirteen cases of unilateral renal malignant disease and associated tuberculosis were reviewed. A case of renal tuberculosis on the right side and hypernephroma on the left was presented. Evidence was offered toward the supposition that the original lesion in the left kidney was of tuberculous origin. Ten of these cases have been reported since 1925. This indicates that one must consider the coexistence of these lesions in the urinary system with more than passing interest.

Horseshoe Kidney.—Sorrentino [9] had occasion to operate on 2 horseshoe kidneys, 1 of them affected with hydronephrosis and the other with tuberculosis. In the first case the pyelogram revealed the characteristic inward rotation of the calices, with marked dilatation of those on the left side. The image of the ureters began at the lowermost part of the shadow of the renal pelves, and both ureters, shorter than normal, followed a course converging from above downward and from without inward. The bilateral pyelogram led to a preoperative diagnosis of hydronephrosis in one half of a horseshoe kidney on the left side, for which the author performed nephrectomy by the lumbar route.

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8. Keen, M. R.: Associated Renal Tuberculosis and Malignancy, Am. J. Surg. **25**:467 (Sept.) 1934.

9. Sorrentino, Michelangelo: Contributo alla chirurgia del rene a ferro di cavallo, Arch. ital. di urol. **11**:262 (April) 1934.

In the second case no pyelogram was made, owing to the patient's refusal to permit it, but the indications for removal of the right kidney were so clear that the author removed it; it was discovered at operation to be a horseshoe kidney in which the isthmus was composed of parenchymal tissue. In both cases uneventful recovery followed operation.

Sorrentino expressed the opinion that the majority of fused kidneys produce no symptoms and are discovered only by accident at necropsy. In his two cases neither patient had the slightest trouble from the malformation until urinary disturbances began, in one case four years, and in the other one year, before observation.

The most efficient aid in diagnosis is the pyelographic image, which reveals the sagging of the renal pelves, their approach to the median line, the indistinct image of the isthmus, the enormous obliquity of the two renal masses from above downward and from without inward and also the divergence of the ureters from below upward, which results anatomically from the rotation of the renal hilus. This sign is not always clearly revealed, but when it is present it has great value.

The deformation of pelves and ureters is seen particularly well in sagittal projection, which causes the shadow of the pelvis to appear elongated, with variations of caliber at different levels and with the calices oriented to the right or to the left or upward in the form of rounded stumps; they are nearly always dilated and abnormally swollen. The pyelogram shows how the ureter starts from the lowermost and most median point of the shadow of the renal pelvis.

As regards treatment, nephrectomy is the method of choice. Sorrentino insisted on the impropriety of calling such a procedure a heminephrectomy, since the removal of one side of the horseshoe mass is in reality a true nephrectomy, the only difference from the usual nephrectomy being the greater difficulty of exteriorization because of the fixity of the organ and the greater operative dangers owing to its greater vascularity and the presence of the isthmus. The transperitoneal approach is to be condemned and should never be used in cases diagnosed before operation.

In performing symphisiotomy it is important to expose the isthmus completely, and for this its accurate isolation is necessary. Sorrentino advised that the isthmus be sectioned not too far from the kidney to be removed, since this enables the surgeon to use a zone supplied mainly by vessels that have been already tied, thus decreasing the amount of hemorrhage. If the isthmus is thin and fibrous, it should be sectioned vertically and sutured with a stitch or two; but if it is parenchymatous and from 2 to 4 cm. thick, a more precise technic is necessary, extreme care being employed to provide for complete hemos-

tasis before an incision is made; Sorrentino employs a flap which he fixes with two U-shaped sutures. In this way he avoids all hemorrhage.

[COMPILER'S NOTE.—The early clinical manifestations of disease of a horseshoe kidney can usually be recognized when a good clinical history has been taken and a careful physical examination has been made. It is almost universal to find that these patients have gone for years with symptoms that are not properly recognized until a concomitant infection brings the patients to the urologist for examination.

The removal of half of the horseshoe kidney for associated pathologic changes should properly be called heminephrectomy since the two kidneys have become a single organ. It appears that in disease of a horseshoe kidney the best procedure is division of the isthmus, or symphysiotomy, when the isthmus is small and fibrous, but when it is large and composed of true renal parenchyma an operation combining symphysiectomy, nephrolysis, ureterolysis and nephropexy is the one of choice.

Sorrentino has properly called attention to the disadvantages of the transperitoneal approach when the organ can be reached by the extraperitoneal route, in order to avoid peritoneal infection.]

Thrombosis of the Renal Veins.—Hepler [10] reviewed the literature on thrombosis of the renal veins and studied the 40 cases presented therein, in addition to reporting 2 personally observed cases.

Although 30 of the 40 cases studied were reported as clinical observations and in 22 there were definite symptoms referable to the kidney, and although the syndrome of thrombosis of the renal veins is clearcut, in no instance has a diagnosis ever been made with pathologic confirmation, either by operation or by necropsy.

The subject becomes of some clinical importance because of the possibility of relief by surgical measures when one considers that in half of the cases the thrombosis was unilateral and that in many instances the hemorrhagic infarction was the predominant clinical lesion, despite the fact that in other cases the primary disease overshadowed it. Undoubtedly recovery from the associated disease is prevented by the onset of the infarction, and its early recognition and treatment would modify the outcome in a number of cases.

A classification of thrombosis of the renal veins is submitted; this is based on the origin of the thrombi and the conditions attending their growth. In regard to the presence or absence of infection in the thrombi, the terms suppurative and nonsuppurative are suggested in place of the ones commonly used, septic and aseptic. Practically all thrombi start on the basis of infection and are associated with some

10. Hepler, A. B.: Thrombosis of the Renal Veins, J. Urol. **31**:527 (April) 1934.

degree of thrombophlebitis or bacterial injury to the intima, either in the capillaries or in the veins. There may be no active infection or suppuration in the secondary extension to the renal veins, but at its source the thrombus arises from phlebitis. Therefore, it seems better to designate the so-called aseptic thrombi as nonsuppurative and the definitely infected thrombi as suppurative. A complete analysis is made of the pathologic and clinical features of the cases reported.

Hepler's first case was one of postscarlatinal thrombosis of the vena cava which evidently existed for some time with the establishment of a collateral collection. Visceral involvement was late and started as a hemorrhagic infarction of the left kidney from a secondary thrombus in the left renal vein.

Recovery after removal of the left kidney was prevented by secondary thrombosis of the right renal vein ten days later. However, the marked improvement following nephrectomy indicates the feasibility of surgical intervention, even in the presence of extensive extrarenal thromboses, if the condition is unilateral, as it is in half of the cases reported, and if the infarction is not overshadowed by the primary or associated disease. The fact that this lesion presents a definite clear-cut syndrome consisting of sudden onset of hematuria, pain and tenderness in the lumbar region and rapid progressive enlargement of the kidney should insure its more frequent clinical recognition. With this presumptive evidence, the additional cystoscopic findings of unilateral bleeding, reduction or absence of function and enlargement of the outline of the kidney with no shadows on excretory urography are diagnostic.

The condition is not uncommon in infants; in them it is usually primary and associated with severe enteritis which overshadows the infarction and precludes the possibility of surgical intervention. At the time of total infarction of one kidney there is frequently beginning capillary thrombosis on the opposite side. However, in older children and adults the thrombosis is usually secondary and unilateral.

Although practically all thrombi arise on the basis of infection, suppurative thrombophlebitis is rare among infants. It usually occurs between the ages of 25 and 50 years and is secondary to severe suppurative lesions of the kidney, either hematogenous or ascending. In the surgical treatment of pyogenic infections of the kidneys the possibility of an infected thrombus in the renal veins as a continued source of blood stream infection must be considered.

Decapsulation.—Lioy,[11] who is an advocate of decapsulation in cases of nephritis, made a clinico-operative study of certain types of

11. Lioy, D.: Considerazioni clinico-operative su alcuni casi di nefrite amaturica e dolorosa, Arch. ital. di urol. **11**:115 (Feb.) 1934.

nephritis in which the chief symptom was pain or hematuria or both of these combined. He observed that pain and hematuria do not in all cases go pari passu, but that in some cases one, and in others the other, of these symptoms predominates, while in a certain number the two are so intimately connected as to be inseparable. As a rule, in the class of cases discussed the lesions are unilateral; in the 8 cases which serve as an illustrative basis for this work there was only 1 in which the second kidney became involved about a month after the involvement of the first kidney.

In all cases operation (decapsulation) has revealed pathologico-anatomic changes in the kidney (enlargement, congestion, fibrous reaction, etc.) and its capsular coverings. The capsule proper was found in every case to be thickened and closely adherent to the organ, so that in some cases extreme caution had to be exercised in its removal to avoid injuring the renal substance and provoking secondary hemorrhages, which are dangerous for the postoperative course. The fatty capsule, too, has been found to be more or less the victim of the pathologic changes of sclero-adiposis. The fibrous connective tissue trabeculae were sometimes in such close connection with the capsule proper as to form a network of plastic adhesions which had to be removed en bloc with the fibrous capsule.

After decapsulation, a systematic search for calculi was made by manual and instrumental palpation. The size of the kidney was always larger than normal, and this was also confirmed by preliminary roentgenograms.

Conservative surgical treatment, that is, decapsulation, brought complete cure in all cases, with permanent good results and disappearance of every disturbance. This operation has proved effective, even in cases in which the morbid process dated back for a year or so. Hence, it seems probable that decapsulation favors the intrarenal circulatory apparatus, and that sclerofibrous changes have not the slightest importance for the perinephrium, whether they are primary or secondary, in the process of chronic nephritis.

The author concludes that nephrotomy for exploratory purposes in doubtful cases of calculosis, of which there were 2, did no injury, either mediate or immediate, with respect to operative results beyond prolonging to a negligible extent the time required for operation. All the good results have been maintained from the one to six years that the cases have been under observation, up to the present time. Pyelography was done in only one or two cases in which general and local conditions permitted. In 2 cases the author found that an iopax derivative (known abroad as uroselectan B) administered intravenously had a remarkable hemostatic action in nephrorrhagia and arrested hemorrhage instantly.

A long and comprehensive bibliography accompanies this article.

[COMPILER'S NOTE.—Renal decapsulation has received preponderant study in the literature, particularly since the work of Edebohls, who reported more than 100 cases of bilateral renal decapsulation for Bright's disease. This work, however, has not withstood the test of time, although the procedure has its indications and good results have been obtained in some cases. It has been proved by necropsy in some cases in which the patients had been subjected to this operation that the capsule proper of the kidney will regenerate within a certain period of time, and therefore the procedure seldom has a permanent curative result.]

Nephropexy.—Strode [12] described the operation of suspension of the kidney by the use of fascia lata. The kidney was exposed by an oblique incision. It was freed of all perirenal tissue down to the capsule and drawn up to its normal position. A strip of fascia lata, from 8 to 10 inches (20 to 25 cm.) in length and ¾ inch (1.9 cm.) in breadth, was then obtained from the leg. After it was cleansed of all adherent fat, the strip of the fascia was passed around the lower pole of the kidney, beneath the capsule. It has seemed unnecessary to suture the kidney or the capsule to the fascial strip. Chromic catgut was used in suturing the overlapped fascia. The incision was closed in the usual manner. No attempt was made to close the defect left in the fascia lata, as previous experience has shown this to be unnecessary. Careful hemostasis is imperative to prevent subsequent hematoma, and as an additional safeguard a rubber tissue drain through a stab wound below the line of closure is advisable. Strode stated that while neither a sufficient number of cases nor the test of time has made the operation as described one of proved merit, the underlying principles have been so well proved as to make the element of error negligible.

Renal Function.—Walters and Counseller [13] stated that the ability of the body to develop an adequate renal reserve is shown by the remarkable hypertrophy which takes place in a solitary kidney or in a remaining kidney following nephrectomy. In the presence of stones in the kidney or ureter and incomplete obstruction producing hydronephrosis the various tests of renal function do not give accurate indexes of the function of the kidney. Much valuable renal tissue may therefore survive long periods of partial or incomplete obstruction. This difference between the actual ability of a kidney to function and that indicated when tests are made may be accounted for by the fact that excretion, on test, is interfered with by the resting state of

12. Strode, J. E.: Kidney Suspension by Use of Fascia Lata, J. Urol. **32**:171 (Aug.) 1934.

13. Walters, Waltman, and Counseller, V. S.: The Restoration of Renal Function, J. Urol. **31**:649 (May) 1934.

glomerular activity noted by Richards, by pyelovenous backflow and by the uncertain reflex action of a stone in the kidney or the ureter.

The return of the excretory renal function following removal of stones in the ureter and kidney in cases of unilateral or bilateral renal injury, as well as the rapid return to normal of a dilated ureter and renal pelvis after removal of an obstruction, is remarkable. The rapidity with which function of the kidney returns depends on the presence of sufficient renal parenchymal tissue which is anatomically and physiologically sound, provided complete relief of the obstruction and adequate control of the infection can be obtained.

It is advisable to remove stones in the ureter or kidney or to remove other obstructing lesions before extensive destruction of the renal parenchyma takes place, especially when a solitary kidney is present. When there is no appreciable return of renal function, as evidenced by increasing excretion of phenolsulphonphthalein and reduction in the value for blood urea, and urinary obstruction has been completely relieved, one has presumptive evidence that serious injury to the kidney has occurred.

Herbst and Baumrucker [14] described a new colorimetric test for renal function using intravenous injection of diodrast.

> The test is performed as follows: a specimen of urine containing excreted neoskiodan is diluted to 1000 c.c. One half cubic centimeter is placed in a pyrex test tube and evaporated to dryness; three drops of a saturated solution of potassium nitrate are added, and again evaporated to dryness; 2 cc. of concentrated sulphuric acid are added, and the whole is cooked and heated. It is then cooled, water added, cooled again. It is then shaken with 2 c.c. of chloroform and compared to a colorimeter. The entire procedure is performed in the same test tube from evaporation to color comparison and does not take more than seven to ten minutes.
>
> The color scale may be made by dissolving 100 mg. of iodine in 128.5 c.c. of chloroform and adding 0.1 c.c. of this solution for each 5 per cent, diluting up to 2 c.c. with chloroform.
>
> The acidified iodine chloroform solution has a slightly deeper shade than the plain iodine chloroform solution. This can be corrected by layering a few cubic centimeters of water, acidified with sulphuric acid, over the iodine-chloroform solution. . . . This test, unlike the phthalein test, can be performed on bloody urine. The urine is diluted to 1000 c.c. to have it correspond more closely to the phthalein test. However, in children where only one-half of an ampoule is used, it may be diluted to 500 c.c. instead and performed as described.

Pyelonephritis.—Rose [15] stated that in cases of postpartum pyelonephrosis with retention of urine in which catheterization is indicated

14. Herbst, R. H., and Baumrucker, G. O.: A New Colorimetric Test for Renal Function Using Intravenous Iodine Preparations: A Preliminary Report, J. Urol. **32**:131 (Aug.) 1934.

15. Rose, D. K.: Postpartum Pyelitis of Pregnancy: Treatment of Certain Cases Without Use of Ureteral Catheter; Explanation Based on Physiology of Bladder, Am. J. Surg. **25**:394 (Sept.) 1934.

on account of either dysuria or toxicity he met with two entirely opposite types of function of the bladder. Either may exist separately, or the two may coexist to any degree. The bladder showing a relatively fixed, compensated wall back of a physiologic block, motor and sensory, of the external sphincter following parturition, if of sufficient degree, requires continuous drainage when indicated by reason of infection. Such drainage reduces, primarily, infection of the bladder and, secondarily, the urethral, pelvic and renal infection by facilitating urinary flow through a decompressed and perfectly drained bladder. Intermittent catheterization in such a bladder traumatizes in the presence of imperfect drainage and, therefore, tends to generalize or to diffuse the infection. The instillation of irritative preparations into such a bladder is contraindicated. If a sufficient degree of altered function of the organ occurs, continuous drainage is indicated until perfect function is restored. The bladder with inhibited or functionally weakened walls and with normal tone of the sphincter following operation requires only intermittent catheterization.

Sisk, Wear and Cummings [16] stated that acute pyelonephritis may cause great destruction of the cortex of the kidney and reduction in function. The inflammation in the wall of the pelvis and ureter and in the peripelvic and periureteral tissues may interfere with drainage early in the course of the disease by diminution in the caliber of the lumen and by lessening of peristalsis. Marked dilatation in the pelvis and ureter may occur without demonstrable evidence of stricture. Great stasis of urine may occur, as evidenced by an emptying time of seventy-five minutes in 1 case which was reported. This increases the intrarenal pressure and increases the tendency of the infection to invade the cortex. Nephrostomy offers a means of giving constant and complete drainage and should be carried out before great renal damage has occurred. Drainage may be temporary or permanent, depending on the progress of the case. In many cases nephrostomy will conserve renal function, and in some cases it will save the patient's life.

Perinephritic Abscess.—Shane and Harris,[17] after reviewing the literature and studying the roentgenograms made in 40 cases in which operation was performed for perinephritic abscess at the Mayo Clinic, concluded that the roentgenographic signs of perinephritic abscess must be considered as a valuable adjunct in the diagnosis of this condition. The shadow of the psoas muscle was obliterated to some extent in all cases; some abnormality of the renal shadow was found in 33 cases (80.2 per cent); scoliosis was found in 18 (28.1 per cent) of the 32

16. Sisk, I. R.; Wear, J. B., and Cummings, E. F.: Nephrostomy in Pyelonephritis, Am. J. Surg. **25**:451 (Sept.) 1934.

17. Shane, J. H., and Harris, Milo: Roentgenologic Diagnosis of Perinephritic Abscess, J. Urol. **32**:19 (July) 1934.

cases in which roentgenologic examination of the thorax was made. In 22 cases (55 per cent) an associated pathologic condition was found at operation, stones being present in 17 cases (40.2 per cent). The frequency with which obliteration of the shadow of the psoas muscle occurs on one or both sides and the frequency with which some degree of scoliosis is found in the course of routine roentgenography diminish to some extent the clinical value of these data. For instance, the shadow of the psoas muscle was obliterated on one side in 10 per cent of cases and on both sides in 3 per cent. Definite scoliosis was present in 3 per cent of cases, but there were several other roentgenograms in which it occurred, in the opinion of some observers; according to others, however, it was absent. The roentgenograms were studied in a series of 50 cases of renal calculi, and obliteration of the psoas muscle, or scoliosis, was found to some extent in over 30 per cent of these cases. The roentgenologic signs of perinephritic abscess, especially obliteration of the shadow of the psoas muscle or scoliosis, do not necessarily indicate the existence of perinephritic abscess and therefore cannot be regarded as pathognomonic. They have a relative importance, however, when considered in conjunction with the clinical manifestations of the disease, which is increased when coincident scoliosis and obliteration of the psoas muscle are observed.

Paranephritic Abscess.—Brown [18] reported in detail his third case to prove that there exists a type of traumatic abscess of the back which involves the contents of the paranephric space and which is the result of trauma to the muscle accompanied with hemorrhage. The first result of the trauma is interstitial myositis in which, if infection follows, small abscesses form; these may coalesce and, with the infected hematoma, form a large abscess. This type of abscess is distinct from the abscess involving the perirenal fat and might more properly be designated paranephric than perinephritic abscess.

Tumors.—Bergendal [19] reported a case of carcinoma of the ureter. He collected the reports of 26 additional cases from the literature and combined these cases with the 49 cases previously analyzed by Rousselot and Lamon and reviewed the entire group, a total of 76 cases. Forty-three of the patients were men and 33 were women. Such a distinct predominance of men was not noted in earlier series. The age of 1 patient was not stated, but the age distribution of the others was as follows: 30 to 39 years, 4 patients; 40 to 49 years, 18; 50 to 59 years, 20; 60 to 69 years, 22; 70 to 79 years, 9, and 80 to 89 years, 2.

18. Brown, Alfred: Traumatic Infected Interstitial Myositis as a Cause of Paranephritic Abscess, J. A. M. A. **102**:2096 (June 23) 1934.

19. Bergendal, Seved: Clinical Study of Malignant Tumors of the Ureter: An Operative Case of Ureteral Sarcoma, Acta chir. Scandinav. **74**:179, 1934.

The youngest patient was 30 years of age and the oldest, 89. According to Bachrach, carcinoma of the ureter occurs at a relatively early age compared with malignant tumors of other organs. In this series 22 of 75 cases (29 per cent) were in persons under 50 years of age. In 41 cases carcinoma was found in the right ureter, and in 35 cases it was in the left ureter. Sufficient information for judging what part of the ureter was the seat of the carcinoma is given in 72 cases, and the distribution is as follows: In 13 cases it was in the upper part; in 10, in the middle part; in 7, at the crossing of the iliac vessels, and in 39, in the lower part; in 2 cases practically the entire ureter was involved, and in 1 case there was a multiple localization in which no definite primary tumor was indicated. A striking feature is the great number of tumors which were found in the lower part of the ureter, where more than one-half were localized. This preference for the lower part of the ureter is well known from previous comparisons. In no fewer than 12 cases the growth either belonged to the ureteral orifice itself or had penetrated the opening so that it could be detected with the cystoscope. Macroscopically the ureteral carcinomas differ widely in appearance. Three types of ureteral carcinoma are most common. The first is the sharply outlined tumor which varies in size from that of a pea or cherry up to that of a pigeon's egg and which fills the lumen and springs from the ureteral wall by a not infrequently narrow pedicle; the surface may be smooth, moderately uneven, split up or papillomatous and cauliflower-like. In the second, or the infiltrative, type the growth invades the ureteral wall for a shorter or longer distance, mostly circularly, constricting the lumen to a greater or lesser degree. If only a short part of the ureter is involved, it may be difficult to determine macroscopically whether a benign stricture or a malignant process is the source of the trouble. On the other hand, cases have been described in which the tumor tissue advances and infiltrates a large portion of the ureter. In the third, or multiple, type the gross appearance may so nearly resemble the picture of multiple papilloma that it is surprising when the malignant nature of the process is discovered at the microscopic examination or manifests itself by metastasizing via the lymph passages. The microscopic structure of carcinoma of the ureter may vary. Histopathologic data were given in 75 of the cases; there were 38 cases of papillary carcinoma, 12 of squamous cell carcinoma, 20 of carcinoma simplex solidum medullare, 3 of adenocarcinoma and 2 of transition cell carcinoma. Exactly half of the cases were of the papillary type. Some of the papillary carcinomas, however, also presented flat epithelial cells. Areas of a distinctly papillary structure were also found often in the tumors in the other groups. Keratinization was observed in at least 2 of the squamous cell carcinomas. The great frequency of papillary carcinoma

has been pointed out by several authors. Carcinomas of the ureter may disseminate in two ways: namely, by implantation and by metastasis by way of the lymphatics. Bergendal stated that there are reports of necropsy in 32 of the cases of ureteral carcinoma; in 22 of these metastasis is mentioned. In at least 1 case metastasis of the lymphatic glands was found at operation. The topographic distribution of metastasis found at necropsy was as follows: in 20 cases it was in the lymph nodes; in 11, in the liver; in 7, in the lungs; in 3, in the osseous system, and in 2, in the pancreas. Among the 76 cases of ureteral carcinoma under review, concretions appear to have occurred in 8 cases, or 11 per cent. Bergendal stated that as in cases of renal tumor the most important symptoms in cases of tumor of the ureter are hematuria, palpable tumor and pain. Of these three symptoms, hematuria, that is, the macroscopic form, may undoubtedly be said to be the most important. Bachrach stated that hematuria occurs in about 45 per cent of all the cases of tumor of the ureter; according to Tiitinen, it is found in about 70 per cent of the cases of carcinoma of the ureter. Bergendal found hematuria mentioned in 54 (75 per cent) of the 72 cases. Pain is also a common symptom of carcinoma of the ureter. Mention is made of pain in 49 of the 72 cases (68 per cent). A study of the literature also shows that particularly during recent years nephro-ureterectomy has been the surgical procedure adopted in most of the cases of malignant tumor of the ureter. This extensive operation has often been performed in one stage. Against this procedure it may be objected that it is a serious operation, especially for debilitated and elderly persons. In the 27 recent cases of carcinoma of the ureter the reports of which have been collected by Bergendal the operation was performed on 10 patients. Of these, no fewer than 4 died after the operation. Bergendal stated that complete nephro-ureterectomy in one stage is regarded as the normal method for the patient whose condition does not directly contraindicate so extensive an operation. Follow-up reports are available only for some of the cases in which operation was performed. Most of the patients died of metastasis or local recurrences a short time after the operation. Only in 6 cases was there a report to the effect that the patient was healthy one year or longer after the operation. At present, therefore, Bergendal feels that the results of the therapy in cases of malignant tumor of the ureter are not encouraging.

Uretero-Intestinal Anastomosis.—Higgins [20] presented a new technic for simultaneous bilateral transplantation of the ureters into the rectum, in which the normal course of the urine and continuity of the ureter

20. Higgins, C. C.: Aseptic Uretero-Intestinal Anastomosis, J. Urol. **31**:791 (June) 1934.

are preserved until after the formation of a new channel between the ureter and the rectosigmoid. The rectum is exposed and the ureter is dissected out and transplanted without disturbing the bladder. Several days later, at a second operation, the ureter is separated from the bladder, and the lower end is ligated.

The procedure is attended by no interruption of renal function during the establishment of the new channel between the ureter and the intestine. The mortality in experimental animals has been practically negligible. There has been almost complete absence of peritonitis and acute renal infection. The immediate results in 8 clinical cases have been unusually satisfactory, but insufficient time has elapsed to warrant any statement as to the ultimate results.

BLADDER

Tumors.—Barringer [21] reported the results in 78 controlled cases of carcinoma of the bladder, which were selected mainly from the cases of patients treated by radium at the Memorial Hospital during the past eighteen years. Of the 78 tumors, 48 were graded according to the scheme of Broders. Nine were of grade 1; 24, of grade 2; 14, of grade 3, and 1, of grade 4. In 55 cases the pathologist made an attempt to determine whether the tumor was radiosensitive; 27 tumors were thought to be radioresistant and 28 were considered radiosensitive. Barringer stated that the suprapubic operation with radium implantation is a relatively benign operation. In his first 109 consecutive cases, 4 patients died in the hospital, an operative mortality of 3.6 per cent. In 179 consecutive cases the operative mortality increased; 13 patients died in the hospital, giving an operative mortality of 7.2 per cent. Barringer stated that if it is considered that in the majority of these cases, from the surgeon's standpoint, the condition was inoperable (if one excludes total cystectomy), it will be realized that this is a low mortality. In 7 cases he performed a second cystotomy and radium implantation, while in another case he opened the bladder three times in a vain attempt to control the growth. In 1 of these 8 cases death occurred in the hospital after operation. The great majority of patients were between the ages of 50 and 60 (33 patients) and 60 and 70 years (25 patients); 1 patient was between 30 and 40 years and 4 were between 70 and 80 years. A patient was not considered well unless he had been without symptoms for a sufficient length of time, a year or more, or unless the bladder had proved to be free from tumor by cystoscopic examination or as seen through a cystotomy wound (this operation being done for some complicating process). Thirty-one patients were well after from

21. Barringer, B. S.: Carcinoma of the Bladder, Surg., Gynec. & Obst. **58**: 867 (May) 1934.

five to ten years; 10 patients, after from ten to fifteen years, and 1 patient after from fifteen to twenty years. Barringer stated that the size of the tumor has no relation to the curability; the size and the position of the base have a direct relation to whether the growth can be controlled. A tumor may fill the bladder and yet may be pedunculated and attached to the wall of the bladder by a very small base. Such tumors are, of course, favorable for treatment by radium implantation. It is interesting to note that in 74 cases in which the size of the base was given, all but 37 of the tumors had a base larger than 6 sq. cm.; 4 were recorded as extensive, and 7 had a base larger than 30 sq. cm. Barringer has classified the tumors as to site into 4 divisions. The first group included tumors of the base of the bladder, touching the trigon, ureters or internal urethral orifice. There were 48 such tumors, a large majority. Of the others, 15 were on the lateral walls, 8 were on the base back of the trigon, and but 2 involved the vault of the bladder. In 5 cases the site was not given. The fact that in a large majority of cases the tumor was situated on, or adjacent to, the trigon makes the operation so signally difficult.

Exstrophy.—Marion [22] stated that he has had occasion in no less than a dozen cases to close a ruptured bladder in a female and to reconstruct the urethra by a simple procedure, the results of which have stood the test of time. In his earlier cases this procedure consisted of taking a tubular graft of mucosa from the vagina and placing it in a tunnel excavated between the bladder and the exterior surface of the body. This was done by means of a trocar, through which was passed the vaginal mucosa which was wrapped around a catheter. More recently he has found that as good results can be obtained by a simple tunneling and insertion of a catheter, without the use of a graft, the only difference being that a little longer time was necessary for epidermization of the tract thus formed. Such constructed urethras require continuous supervision over a long period of time. The patients are taught the use of bougies, which at first are passed daily and later at intervals not to exceed three or four weeks, a little dilation occasionally being necessary. The new urethras are permeable, and they also prove to be absolutely continent, the continence being pathologic, resulting from the enclosure of the new canal in tissues which are more or less fibrous. The method is invaluable for use in cases in which the urethra has been completely destroyed during parturition. Recently, Marion used the method in a case of exstrophy of the bladder, cure resulting. If the early results are maintained, this condition will cease to be the redoubtable malformation which it has been considered. The operation should

22. Marion, G.: De la constitution d'un urètre continent chez la femme et de son emploi dans l'exstrophie vesicale, J. d'urol. **37**:393 (May) 1934.

not, however, be attempted on a child less than 10 years of age. A flap taken from the achilles tendon is wrapped, with its raw surface outward, about a no. 18 Pezzer catheter and is drawn through an excavation which has been made with a trocar between the vagina and the bladder; if the child is a girl, this commences immediately above the vaginal opening and terminates at the bottom of the bladder, behind the interureteral line; the flap then assumes automatically the correct position. The margins of the bladder are now freed by an incision, which passes all the way around the organ; the latter is separated from the deep parts, and the muscular wall is removed over a tract from 2 to 3 cm. long. This gives rise to considerable bleeding, which must be controlled by clamps and tampons. When the bladder has been freed, care must be taken to unroll its edges, which have been rolled up. This is done by sectioning the tissues on the external surface of the bladder to from 1 to 2 cm. from its edges, to make the walls of the bladder susceptible of ready coaptation. The edges of the bladder are sutured transversely or vertically, whichever is easier, reserving an orifice for the placing of a second catheter to deviate the urine. The sheath of the large rectus muscle is then incised longitudinally as far as possible, and the aponeurosis, which forms the anterior wall of the sheath, is separated in such a way that it can be turned back toward the median line and sutured to the opposite side except at the point where the Pezzer catheter is placed. The skin around the bladder is sutured by means of a silver wire and is drawn toward the median line. In some cases flaps may be necessary to secure a complete covering. These may be obtained by undercutting about 3 cm. from the edges of the skin on each side, the two extremities of both flaps remaining adherent to the tissue beneath, while the flaps themselves are drawn together to meet in the median line; the gaps left by the undercutting close later by second intention. The Pezzer catheters must be kept in place as long as possible and must remain patent; this is accomplished not by injections into the catheters but by the use of bougies. They should be changed only when they cease to be patent; if possible, the lower one should not be disturbed for two weeks in order to allow the graft to adhere. After the urethral tract is well established and can be easily catheterized, the upper fistula is closed. In male children the new urethra will go from the bladder to the perineum; the dissection of the lower part of the bladder will pass above the verumontanum and separate the urinary part completely from the genital part. When repair of the exstrophy has been obtained, the upper canal of the penis may be closed, and this new canal will serve only for accomplishing ejaculation.

Vesical Calculus.—Price [23] stated that vesical calculus is rather common in Shantung Province. His report is based on the cases of 126 patients who were admitted to the University Hospital in the last five years. Most of the patients were boys from the country, between 5 and 15 years of age, who began to have symptoms in the spring in the second to the sixth year of life. Characteristic symptoms occur in attacks of increasing length and severity, until finally there are no symptomless intermissions. The etiology of vesical calculus is obscure. Price's study of the incidence appears to lend indirect support to the theory that dietary deficiency, perhaps vitamin A deficiency, is an important causative factor. In his experience, roentgenologic examination is the most informative single diagnostic procedure for stone in the bladder. Demonstration of the presence of a stone in the bladder is not sufficient; the condition of the urethra, bladder, kidneys and body in general should be determined. If severe cystitis or evidence of renal damage is found, operation is best delayed until the condition can be improved. The preoperative, operative and postoperative treatment developed at the University Hospital was described in detail. Its essential features are: adequate preoperative treatment which is based on careful and complete diagnosis; suprapubic lithotomy, the bladder being distended with measured quantities of air; special care that the wound does not become contaminated by vesical contents; anatomic closure of all the layers of the wall of the bladder without drainage; drainage of the bladder for four or five days by means of a catheter carefully placed and securely fastened in the urethra, and attempts to restore the entire urinary tract to normal. A stone which is partly impacted in the prostatic urethra presents special problems. Suggestions are made for dealing with this sort of case.

Foreign Bodies.—The introduction of foreign bodies into the urinary bladder may be either intentional or accidental. Almost every known conceivable substance that the urethra can admit has been introduced into it and subsequently found in the bladder. Most commonly, Kau [24] found lead pencils, wire hairpins, crochet needles, rubber tubing, stems of plants, shirt buttons, shoestrings, glass rods and wire, and recently, more cases were reported in which chewing gums and paraffin wax had been introduced into the bladder. On the other hand, the foreign bodies which were accidentally introduced into the bladder were more commonly found in aged people and consisted of instruments used for the relief of urinary retention. Portions of ordinary or Pezzer catheters, glass catheters, bougies, jaws of lithotrites and similar instru-

23. Price, P. B.: Bladder Stone, Chinese M. J. **48**:462 (May) 1934.

24. Kau, Z. M.: Foreign Bodies in the Urinary Bladder, Chinese M. J. **48**: 475 (May) 1934.

ments composed most of the foreign bodies found in this group during the last century, but with the improvement of our surgical technic and the instruments these accidents have become less frequent. There is a rare group of foreign bodies that may gain entrance into the bladder through ulceration of the vesical wall. These foreign bodies are usually situated or get lodged in the perivesical space; they consist of gauze sponges overlooked at operation, sequestrums from osteomyelitis of pelvic bones, fragments of shells and bullets. As a result of mechanical irritation by a foreign body, infection of the bladder sooner or later takes place. Cystitis, therefore, is a common complication of the presence of a foreign body in the bladder, especially in the chronic and latent cases. With infection, phosphatic incrustation ensues and a stone develops, with the foreign body as the nucleus. Foreign bodies which have rough or irregular surfaces are more susceptible to phosphatic incrustation; this is practically absent or the process goes on slowly in the case of smooth objects such as glass or wax. Foreign bodies which have sharp pointed ends, such as needles and pins, are liable to produce ulceration of the vesical wall and secondary perforation. Sometimes they may escape through this perforation and be discharged to the peritoneal cavity, perivesical space, rectum or vagina. On account of the irritation of the bladder and the accompanying cystitis, disturbances in the act of urination dominate the clinical picture, though in certain cases the foreign body may remain latent and symptomless. Frequency of micturition, painful urination, urgency and tenesmus are the usual symptoms presented by these patients. Hematuria and pyuria are almost always present at one time or another. Acute or chronic urinary retention and incontinence of urine may develop if the foreign body is impacted in the vesical orifice. Pain may be referred to the tip of the penis or to the perineal region. In fact, the symptoms are more or less similar to those of vesical calculus. The treatment depends on the nature and shape of the foreign body. A careful cystoscopic and roentgenologic examination is essential before treatment. In general, it may be described under two headings, the nonsurgical and the surgical. In the nonoperative treatment, foreign bodies, such as catheters, filiforms, rubber tubing, stems of plants, chewing gum, wax and needles may be removed through the operating cystoscope, Young's cystoscope rongeur, the observation lithotrite or Kelly's hollow tube cystoscope with alligator forceps. Care must be taken in removing sharp pointed objects, especially needles, for rupture or injury to the bladder or urethra may occur otherwise. Surgical removal by means of suprapubic cystostomy is indicated whenever nonoperative treatment fails or in the absence of special instruments.

Fistula.—Elaut [25] reported a new method of treatment of vesicovaginal fistulas which meets the requirements better than any other method in cases in which there has been extensive loss of substance. It has been successfully used in two cases.

A method, to be satisfactory, must place the restored wall of the bladder beyond the reach of the least traction that might compromise its continuity; hence the catheter tube used for drainage of urine must be so placed that it does not come in contact with the surface of the vesical wound. It also must protect the sutured wall from the corrosive action of the urine; it must therefore effect drainage at the lowest part of the bladder, so that the bladder may be emptied completely. These conditions are fulfilled in Elaut's transcervical drainage, which is carried out through the anterior wall of the cervix uteri by means of a specially devised curved metal tube which conducts the urine through the vagina and across the perineum into the urinal. When the tube is once in place, the fistula is closed by the standard procedure after the making of a duplication of the vesicovaginal partition. To understand the basis of this method, it is necessary to observe the anatomic relations of the bladder and the cervix. The important points to study are the distance between the anterior vaginal culdesac and the peritoneum of the vesico-uterine space, the point of the bladder that is lowest when the patient is recumbent, the point of contact of the bladder with the cervix, the vessels that might be injured during manipulations inherent in the drainage and the situation of the ureters with reference to the tract of the tunnel. In carrying out his studies on cadavers, Elaut took account of the fact that the fistulous bladder must be regarded as empty. He found that the distance between the vagina and the peritoneum, while varying in different persons, averaged 35 mm. in normal subjects during the sexual period of life. In cases of metritis, perimetritis and parametritis, its length may be 40, 50 or 60 mm., as the result of the enlargement of the uterus caused by inflammation. It is at the level of this region that the bladder and the uterus are in contact with one another at the vesico-uterine partition. The peritoneum lining the space between the uterus and the bladder posterior to this partition is the equivalent in the female of Denonvillier's fascia. It is worthy of note that there is no fat in this space. The only point of contact of the uterus with the bladder is at the cervix. Even when the bladder is empty, the tract making contact is never less than 25 mm. long under normal conditions. On the vesical side of the partition, the contact is in the region in which the greatest transverse diameter is found; this diameter is constant whether the bladder is full or empty;

25. Elaut, L.: De la derivation transcervicale de l'urine dans la cure des fistules vesico-vaginales, J. d'urol. **37**:21 (Jan.) 1934.

it runs from one lateral recess to the other, and it is at about the middle of this tract that the point of contact is to be sought. This line, which constitutes the postero-inferior border of the vesical cavity, is about 40 mm. from the line joining the ureteral meatuses. By restricting the incision rigorously to the median line, one can be absolutely certain that the drainage tube will puncture no vessel, however small. The operation is divided into two stages: exposure of the vagina and the placing of the drainage tube. The exposure must be as wide as possible, and in some cases it may be necessary to incise the perineum. To admit the tube, the cervix may sometimes have to be slightly dilated.

Vesical Pressure.—Watkins [26] investigated the condition of the detrusor muscle in cases of injury to the lower part of the spine by estimating the vesical pressure. For comparison, studies were made of the normally innervated bladder, and as a result Watkins concluded that although definite information concerning the condition of the innervation of the bladder can be obtained by making careful estimations of the vesical pressure most of the information can be derived from simpler measures and from clinical observations.

A vertical glass tube, 4 mm. in internal diameter, was used as a water manometer. It was connected by a T-tube with a reservoir filled with a 1:4,000 solution of mercuric oxycyanide and an inlying catheter. Fifty cubic centimeters of fluid was introduced, and readings were taken at the first sensation of filling, at the first attempt at urination, either from actual contraction of the detrusor muscle or from abdominal straining, and then after each further addition of 50 cc. of fluid. The results in 24 cases in which there was normal innervation of the bladder are discussed and compared with those obtained by other investigators.

Watkins concluded that with the use of the water manometer it should be simple to differentiate between rises of pressure resulting from abdominal straining and those which result from contraction of the detrusor muscle. Furthermore, it should be possible to demonstrate contraction of the detrusor muscle at any observation on a normally innervated bladder, and such contraction should cause a pressure of about 150 cm. of water or more, which is approximately twice as great as can be caused by abdominal straining alone.

Three cases were studied; these were cases of urinary retention from lesions of the spinal cord with disturbance of the sacral segments. Important evidence can be obtained by readings of vesical pressure, particularly in regard to contraction of the detrusor muscle, while the

26. Watkins, K. H.: The Clinical Value of Bladder Pressure Estimations, Brit. J. Urol. **6**:104 (June) 1934.

nature of the pressure curve "at rest" and the point of first sensation are of much less value.

However, it is doubtful if the same information cannot be obtained by simple clinical methods. At cystoscopic examination it is possible to determine the point of first sensation and the capacity of the bladder. By watching the urinary stream after excluding the presence of obstruction, it is possible to determine the presence of powerful contraction of the detrusor muscle. If the stream is forcible, of wide caliber and continuous, evacuation must be the result of contraction. In a paralyzed bladder there are much straining, poor force, narrow caliber and interruptions coincident with the taking of a deep breath, which hinder abdominal action and straining.

At the present time it does not seem justifiable to make any very vigorous claims for the introduction into routine clinical practice of a method which provides little more information than can be derived by simpler methods.

(To be Concluded)

Correspondence

CONTINUOUS INTRAVENOUS INJECTION

To the Editor:—In the April issue of the ARCHIVES OF SURGERY (**30**:685, 1935) there is an article entitled "Experimental Pulmonary Embolism Associated with Venoclysis" by Mervin J. Rumold, of Kansas City, which seems to discredit the use of continuous intravenous injections. For several years I have been advocating and using continuous intravenous injections, particularly in connection with surgical procedures, and I have written several articles on the subject.

The experiments of Dr. Rumold appear to have been carefully performed, but in my experience his conclusions do not seem applicable to clinical work for the following reasons:

1. The vein used by Dr. Rumold in all of his experiments (listed in the six tables) was the external jugular vein in a dog, except in 2 experiments in which the saphenous vein was used. In a dog the external jugular vein is large and practically supplants the internal jugular vein, which is always small and almost negligible in function. The total number of dogs experimented on was 19. After each of the 19 experiments either pulmonary infarcts or pulmonary thrombi resulted, usually both. A clot in the large external jugular vein of a dog would probably be quickly transported to the lung because of the size of the vein and the very short and direct communication with the vena cava. I know of no clinical instance in which a continuous intravenous injection has ever been given through the jugular vein. In the 2 experiments in which the saphenous vein was used, it is said that "Considerable difficulty was encountered in keeping the dogs quiet." On the whole, then, so far as the vein is concerned the conditions that obtained in the experimental work of Dr. Rumold are quite different from those in the clinical use of intravenous methods. Even in the 2 experiments in which the saphenous vein was used, the dogs obviously could not be well restrained. Clinically, in continuous intravenous infusion, or so-called venoclysis, the arm or leg into which the solution flows is kept still, usually by a small splint. If a patient were to use the arm or leg through which continuous intravenous injection was being given, a clot not only would be more readily formed from injury to the intima of the vein but would be more readily forced into the circulation.

2. The solution that was used in almost all of Dr. Rumold's experiments was a 10 per cent solution of dextrose. As was shown by Matas in his original contribution on continuous intravenous injections, a 5 per cent solution of dextrose is about isotonic with the blood. Ringer's solution is known to contain most of the important electrolytes of the blood in the approximate proportion in which they are found in the blood serum. A 10 per cent solution of dextrose is distinctly irritating to the vein, though doubtless it can be employed for a few hours with comparative safety. When it is desired to stimulate the function of the kidneys or to reduce edema, a 10 per cent solution of dextrose may be used, but the fact that the stronger solutions of dextrose are one of the remedies for sclerosing varicose veins shows it is much more likely to cause injury to the veins than the isotonic 5 per cent solution. Naturally, the insertion of a needle, and still more of a cannula, into a vein may induce a clot at the point of trauma. That this is not a frequent or serious occurrence, however, is shown by the common and innocuous practice of removing the blood from a vein for a Wassermann test or

by the intravenous administration of various drugs. Rarely is the vein occluded in these instances, or, if it is occluded, the smaller caliber of the vein and the distance from the vena cava make it probable that the clot will become adherent to the intima and eventually be absorbed. Often veins that have been occluded with thrombi resolve and become permeable again. It is well known that even in the extensive thrombosis that occurs after phlebitis pulmonary emboli are very uncommon, though they do occur. The injection of sclerosing material into large varicose veins seems to afford a much more fertile field for pulmonary emboli than could possibly occur from the slow injection of an isotonic solution into a small vein, yet such an occurrence is rare.

3. The employment of the apparatus which Dr. Rumold illustrates is distinctly favorable for pulmonary thrombosis. The so-called Murphy "drip method" of administering fluid into the rectum is convenient for determining the rate of flow, and any air that is carried into the rectum is harmless. Why this procedure should be adopted for intravenous injection, however, I have never been able to understand, because it is well known that the injection of air in any considerable quantity into the venous system is injurious and often fatal. It may plug a branch of the pulmonary arteries and form a thrombus, while the original cause of the thrombus —the air—may be readily overlooked in the necropsy. This drip method seems to have for its only recommendation the fact that the rate of injection can be gaged. Even this advantage is more apparent than real. By the use of a narrow buret containing about 500 cc. of solution, the flow of the solution can be regulated fairly accurately so that it can be cut down to as low as 50 cc. an hour with considerable accuracy by quickly noting the changing level of the fluid on the narrow buret. In the drip method, however, the drops must be counted as the pulse is counted, and the size of the drops may not always be the same. If in the glass drip apparatus there is an aperture for air, as in proctoclysis, the air can, of course, readily enter this space, but even if there is no such aperture the rate of flow below the apparatus may become greater than the supply above to the apparatus, which may result in the suction of air into the blood stream. If the patient or animal vomits, strains or becomes congested, the rate of absorption of the intravenous injection would be temporarily slowed down because of the venous back pressure, but when this passes off and the respirations become more rapid the rate of venous flow is increased, and it is easily conceivable that some air may be sucked in because the rate of supply by the drip method is fixed. Even though there may be no direct communication with the outside air, a partial vacuum in the drip apparatus may be induced and air aspirated into the vein. An air bubble coming into the circulation and speeded along by the force of the intravenous injection as well as by the flow of the venous current may readily pass through the right auricle and ventricle and into the pulmonary circulation without being sufficiently large to disturb the action of the heart.

4. Experimental work on dogs is interesting and often uncovers many valuable points, but the results cannot always be directly transferred to man. Thus, for instance, the Koontz fascia lata of the ox seems to have been almost perfect in dogs and is incorporated into the tissues, but in human beings, in my own experience with it, it has been unsatisfactory. In 2 cases the abdominal wound broke open, once nine days and once six days after the operation, and I have had other unfortunate experiences with it. The fascia was recovered in these cases and was shown to be disintegrated.

During the last five years continuous intravenous injection of a 5 per cent solution of dextrose in Ringer's solution has been used at St. Elizabeth's Hospital, Richmond, Va., in about 2,500 patients, the length of the period of administration

varying from three hours to four days. In many of these patients it was used several times. I believe that it occasionally was life-saving. In this period of five years 6,237 patients were admitted to St. Elizabeth's Hospital, and there were 4 deaths from pulmonary embolism. One of the patients, who received 1,000 cc. of a 5 per cent solution of dextrose in Ringer's solution the first day after operation, which was done for acute gangrenous appendicitis, died suddenly seventeen days later while he was up in a chair. Another patient, who was operated on for vesical stone, suprapubic cystotomy being done, received 500 cc. of a 5 per cent solution of dextrose in Ringer's solution the day of operation and died suddenly of pulmonary embolism eighteen days later. A third patient received about 8,000 cc. of a 5 per cent solution of dextrose in Ringer's solution over a period of about three days after gastro-enterostomy and died of pulmonary embolism sixteen days after the operation. This is the only case in which venoclysis can be reasonably considered as a probably causative factor. The fourth patient, who had an exploratory operation followed by roentgen treatments for carcinoma of the ovary with metastases, died two weeks after the operation from pulmonary embolism. She had received no intravenous injection of any kind.

The incidence of pulmonary embolus over this five year period appears to be no greater than that noted when continuous intravenous injection of dextrose is not used. The comparison of the results of venoclysis in 2,500 clinical cases with those of Dr. Rumold's 19 experiments in dogs becomes obvious. I regard continuous administration of a 5 per cent solution of dextrose in Ringer's solution when properly given as one of the greatest aids in many cases, and I should not willingly dispense with it except after some convincing demonstration of its injurious effects.

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